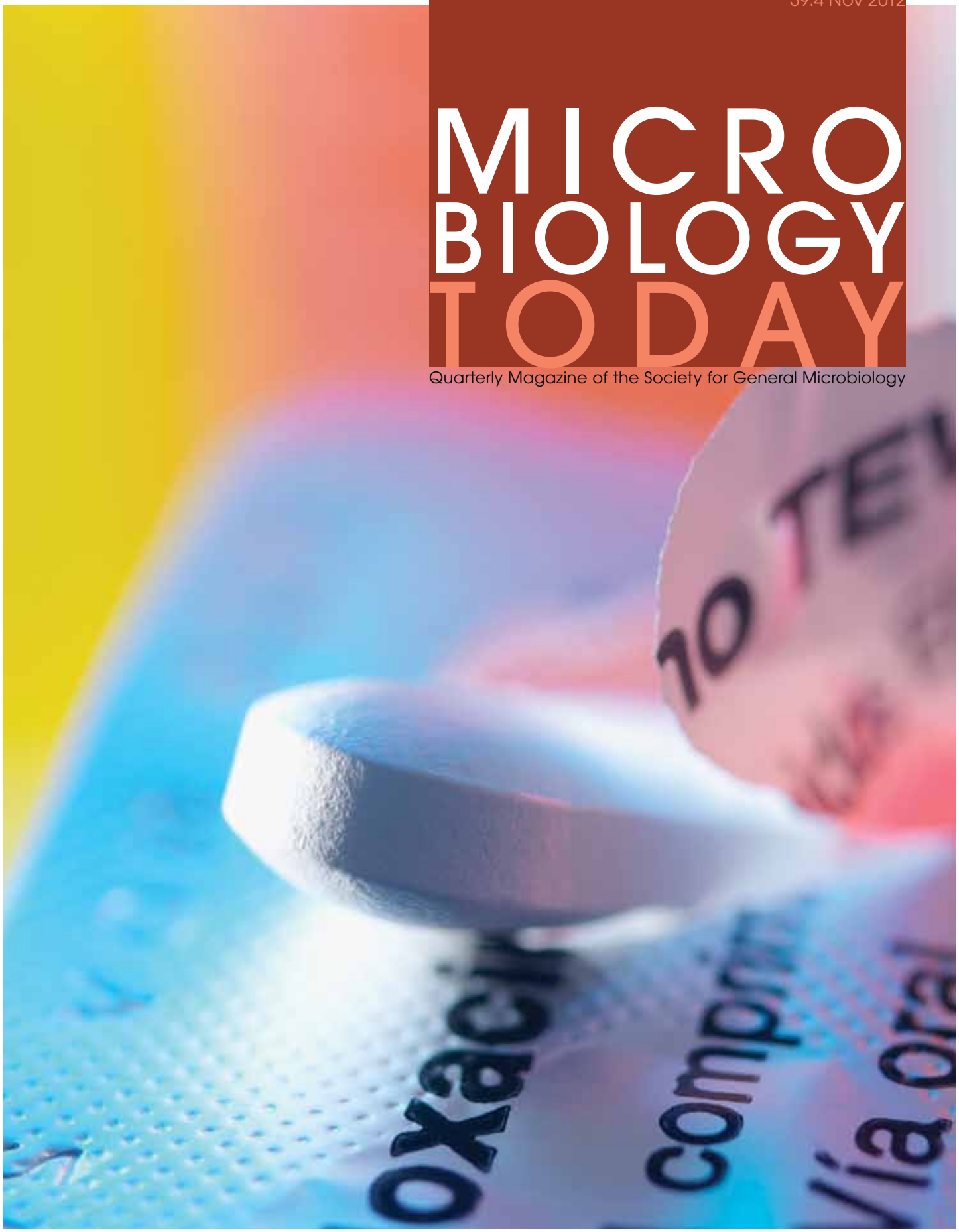
39:4 Nov 2012

MICRO BIOLOGY TODAY

Quarterly Magazine of the Society for General Microbiology



Antimicrobials • Antibiotic discovery then and now • Biosynthetic potential of *Actinobacteria* • Waging war on fungi • Enzybiotics and phages • Drugs from bugs that kill bugs • Flying the flag for 'Antibiotic Action'

EDITORIAL

Welcome to the November issue of *Microbiology Today*. This issue is focused on a subject very close to my heart – antimicrobials.

In 2009, the World Health Organization recognised that antibiotic resistance was one of the three greatest threats to human health. In this issue, we discuss some of the issues related to antibiotics, their use and discovery.

Julian Davies introduces the subject with a discussion of antibiotic discovery and how this has changed since the days of Fleming and Waksman (p. 200). Patricia Veiga-Crespo and Tomas Villa cover the use of bacteriophages and enzymes derived from bacteriophages in food, where they suggest there is great potential for this technology (p. 212). To tackle issues in fungal infection, Neil Gow tells us about a new strategic award from the Wellcome Trust to the University of Aberdeen is to lead a pan-UK consortium in medical mycology (p. 208), and Laura Piddock and Tracey Guise provide an update on the first year of *Antibiotic Action* and the great strides it has made in its first 12 months (p. 239). Helge Bode discusses his work on exploring the symbiotic relationships between bacteria and nematodes that kill insects and how this has led to the discovery of new natural products that have therapeutic potential (p. 216).

Finally, I contributed to this issue myself, describing how we can access the biosynthetic potential of actinomycete bacteria using a range of modern molecular biology techniques, with the potential to access new antibiotics (p. 204).

I'd also like to take this opportunity to thank Hilary Lappin-Scott for all her help and support for *Microbiology Today* during her presidency and to wish Nigel Brown every success in his new role as President. I also used this change in presidency to solicit articles from both! It is encouraging to see SGM taking a proactive role in promoting diversity awareness in microbiology (see 'Marjory Stephenson and me' by Hilary on p. 229) and what we hope will be a regular feature from Nigel as President (p. 193).

I hope you, the readers, will also appreciate the new format of *Microbiology Today*, the SGM staff, in particular Ian Atherton and Dariel Burdass, have worked incredibly hard on the new design, based on what you, the membership, told us. In addition, you will notice the slight adjustments to content. I hope you enjoy this issue and we look forward to hearing any thoughts on the new design.

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REGULARS

Cover **Ciprofloxacin antibiotic pill in a blister pack.** *Tek Image / Science Photo Library*

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society for general Microbiology

FROM THE PRESIDENT

It is a great privilege to have been elected President of the Society for General Microbiology in September and I look forward to serving the Society and its members over the next 3 years.

It is a time of great change in the external environment for learned societies, and Council and the Marlborough House staff will be working hard to ensure that the Society continues to be successful. We will have to meet the demands of open access publication that UK funders are asking for, yet maintain the journal income to support our conferences, our educational provisions, and our many other activities. We have to continue to provide member benefits that are valued.

This would at least maintain the status quo, but there is much more that the Society needs to do. The Society started to modernise its practices under Hilary Lappin-Scott and the appointment of Simon Festing as Chief Executive has accelerated the process. This progress will continue going forward. We have appointed a new Publications Manager who will bring forward a publications strategy for Council's consideration. A new website will be launched early in 2013, which will be more up-to-date and user-friendly than the current site. Marlborough House staff will have the benefit of working with a new members' database, allowing us to be more responsive and tailored to members' needs.

These internal changes are just the start. We have restructured the Committees of Council to serve the new Strategic Plan; we are currently in the process of electing members to these Committees. The Education and Public Affairs Committee and Education Division have been reformed into the Communications Committee and Professional Development Committee to serve the external educational environment (schools, public engagement, etc.) and to help in the continued professional development of our members. In particular, we are concerned with the issues of development of early-career researchers and ensuring that we promote equality and diversity. As outgoing President, Hilary Lappin-Scott has written on gender diversity in the profession in this issue (p. 229), and Council has asked her to be the SGM Diversity Champion.

The Policy Working Group has become the Policy Committee and is engaged in responding to consultations, in developing a policy statement on Sexually Transmitted Infections, and in influencing scientific opinion-formers in Government, funding agencies and elsewhere. Our previous policy statement on Food Security and Food Safety was well received by parliamentarians and other opinion-formers. The SGM presented the policy to the Government's Food Research Partnership. In this issue (p. 226), there is an interview with Professor Ian Boyd, recently appointed Chief Scientific Adviser to Defra, following similar articles with the European CSA and the UK Government CSA.

During my Presidency, I plan for the SGM to engage much more strongly with Government and public bodies, to better represent the discipline of microbiology and to ensure that the relevant science is taken into account in decision-making. Where appropriate, this will be done in partnership with other learned societies. The issues of emerging infectious disease, antimicrobial resistance, vaccination, and a number of other scientific topics relevant to our discipline require continual engagement by members, and relatively new developments, such as synthetic biology, require us to make the scientific information more widely known.

I look forward to leading the Society through these exciting times and would like to hear from any members who are keen to support these endeavours.

NIGEL L. BROWN, President
Email president@sgm.ac.uk

NEWS

NEWS OF MEMBERS

Congratulations to…

STEM Ambassador **MARK FERNANDES** (IFR, Norwich) who has won the CUE East Award for Individual Achievement for his outstanding contribution to public and community engagement;

ROSS FITZGERALD who has been appointed Chair in Molecular Bacteriology at the University of Edinburgh;

IAN POXTON (University of Edinburgh) on receiving a lifetime achievement award from the Anaerobe Society of the Americas for his contribution and dedication to the field of anaerobic microbiology.

The Society notes with regret the passing of **DR DEREK J. BARBARA** (member since 1973), **PROF. HOWARD GEST** (member since 1956) and **PROF. ROBIN J. ROWBURY** (member since 1964).

PART 2 MICROBIOLOGY PRIZE WINNER CONTINUES TO EXCEL

David Butlin, University of Reading

DAVID TAYLOR, who was awarded the SGM prize for the best performance in his Part 2 Microbiology Modules at the University of Reading, has continued to excel in his studies and has gone on to win the Part 3 Biomedical Project Prize in 2012 for his project on '*The role of M protein in torovirus assembly*' with Dr Ben Neuman. David is pictured here with Professor G. Brooks, the Pro-Vice-Chancellor for Teaching and Learning at the University of Reading.

SUCCESS FOR SGM CARA GRANT RECIPIENT

Supporting professional development of microbiologists is one of the core strands of SGM strategy and, in 2011, Council decided to add a new dimension to this by offering sponsorship to the Council for Assisting Refugee Academics (CARA), an organisation which provides much-needed financial assistance to microbiologists who have come to the UK as refugees escaping persecution.

The first grant recipient was Nadje*, who has a PhD in Microbiology from the University of Salahaddin, Erbil, Iraq, and 10 years experience of teaching and supervising students. She is now paving her way to becoming a clinical scientist in the UK. Using the funds, she was able to enrol on the MSc in Molecular Biology of Infectious Diseases at the London School of Hygiene and Tropical Medicine in September 2011, for which she immediately expressed her gratitude; '*I have got the experience and skills and this is my opportunity to get my life and my career back on track*'.

Najde enjoyed the course and performed well while looking after her two young children. She even found time for voluntary laboratory work at St George's Hospital during the summer of 2012 to supplement her CV. The MSc finished with a research project with the support of Nick Dorrell's group.

About CARA

CARA will celebrate its 80th anniversary in 2013 and remains an organisation run by academics working on behalf of fellow academics in need, who are all too often amongst the first to be targeted by state-sponsored violence and repression. SGM was the first learned society to engage in a formal partnership to offer financial support that is committed to a specific academic discipline.

**Nadje is an alias to protect the grant recipient's identity.*

SGM AT ASE

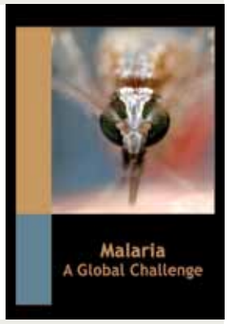
In January 2013, we will be returning to the Association for Science Education (ASE) Conference in Reading.

Tom Ellis (Imperial College London) will be giving a talk on synthetic biology as part of *Biology in the Real World*, James Redfern and John Schollar will be giving practical advice, and the SGM team will be in the exhibition tent (free entry!). If you are going along, drop by to say 'hello'!

MALARIA RESOURCE

Our long awaited fact file *Malaria: A Global Challenge* is now available to order from our website: **www.microbiologyonline.org.uk/teachers/resources**.

Members are welcome to contact our Education & Outreach Officer Vicki Symington (v.symington@sgm.ac.uk) for multiple copies for education or outreach activities.



Guests at the 60th anniversary celebrations. *University of Reading*

60 YEARS OF MICROBIOLOGY AT READING

Well over 100 alumni and other former and current Reading microbiologists gathered on 7 September 2012 to celebrate the 60th anniversaries of the founding at Reading of the first university Department of Microbiology in the UK in 1951 and the introduction of the degree course in microbiology in 1952. SGM was represented by Jane Westwell. A series of talks was followed by a reception and a ceremony to re-name the microbiology building as the Knight building to honour the Foundation Professor B.C.J.G. (Gabe) Knight (1904–1981). A ceremonial plaque was unveiled by a member of his family, and those present signed the Visitors' Book which contains previous entries from six Nobel Laureates, half of the past Presidents of SGM and HM the Queen who formally opened the building in 1992.

'Gabe' Knight came to Reading with an international reputation in microbial nutrition and recognition for the first demonstration of an enzymic activity in a bacterial toxin, i.e. *Clostridium welchii* (now *perfringens*) α-toxin. He made a significant contribution to the founding of SGM, was a member of its first committee, and the first and longest serving Editor of the *Journal of General Microbiology*. He also gave the Marjory Stephenson Memorial Lecture in 1961. On retirement in 1969 he was made an Honorary Member of the Society.

This association with SGM was maintained by Knight's successor Colin Kaplan as joint founding Editor of the *Journal of General Virology*, and this continued through his successor Jeff Almond (Fleming Lecturer, 1985), Jane McKeating (Fleming Lecturer, 1995) and John Grainger (Peter Wildy Prize Lecturer, 2002).

The former Department of Microbiology, now within the School of Biological Sciences, maintains vigorous research programmes in bacteriology and virology, and continues to provide a BSc course in microbiology which includes a field course in Iceland.

For further details see **www.reading.ac.uk/news-and-events/releases/PR464056.aspx**

JOHN GRAINGER

CONFERENCES

SGM Spring Conference 24–28 March 2013

Manchester Central Convention Complex – www.sgmmanchester2013.org.uk

SUBMIT YOUR ABSTRACT and be part of the SGM Spring Conference 2013.

REGISTER TO NETWORK at Europe's largest annual gathering of microbiologists.

SGM Prize Medal Lecture to be delivered by Nobel-Prize-Winning Virologist Harald zur Hausen.

CONFERENCE SNAPSHOT

Metabolic interactions at the host–pathogen interface (25–26 March 2013)

Despite global efforts, diseases such as malaria, sleeping sickness and tuberculosis still affect up to half a billion people each year, and cause more than 2 million deaths. New drugs to combat these diseases are urgently needed. Drugs targeting essential steps in pathogen metabolism represent a promising and relatively unexplored approach for disease control.

There is increasing evidence that the nutritional environment within host tissues has a major impact on pathogen growth and virulence, and that pathogens are able to manipulate host metabolism to promote infection.

Why attend

Speakers at this symposium will review our current understanding of metabolic interactions at the host–pathogen interface, and discuss the prospects of using knowledge of metabolic interactions between host and pathogen to develop novel strategies for disease control. In particular, **Henri Vial** (Université Montpellier II), **Mike Barrett** (University of Glasgow) and **Bill Hunter** (University of Dundee) will explore metabolic targets for disease control.

Bacterial–fungal interactions (27–28 March 2013)

Bacterial–fungal interactions play a pivotal role in agricultural and forestry ecosystems, in food spoilage and plant disease, and in infection of human and animal hosts. They also have a wide range of applications from biocontrol and bioremediation through to food and drink production and the production of novel high-value chemicals.

Why attend

Speakers from a wide range of fields will explore the mechanisms, impact and applications of bacterial–fungal interactions. The symposium will include a presentation by **Reid Harris** (Virginia Tech, USA) on biocontrol of *Chytridiomycosis*, an extremely damaging disease of amphibians.

Networking workshop for early-career delegates (24 March 2013)

Conferences are all about communicating with other scientists, either formally when presenting research or informally when you network with other researchers during breaks, poster sessions or after the conference sessions close. Conferences also offer networking opportunities which can lead to fresh ideas, a new collaboration or maybe even your next job.

Why attend

The networking workshop and supper brings together early-career delegates before the start of the conference. Delegates who attend get to know some friendly faces and also pick up tips and advice on making the most of networking opportunities during the following days. The session is highly recommended by previous delegates:

'…The skills we learnt in the networking event made me feel more confident in approaching other researchers. Being at a conference and having the chance to talk face to face with other researchers in your area really improves your relationship with them and it shortcuts communications compared to building up a relationship by email…'

SYMPOSIA

- Viruses and human cancer: causes to cures
- RNA – so much more than just a genome
- Co-infections & co-colonisation
- New approaches to exploit *Streptomyces*
- Next-generation antimicrobials
- Antimicrobial resistance: are scientists getting the message right?

VIROLOGY WORKSHOPS

- Vaccines and antivirals I Viromics I Assembly and structure I Innate immunity I RNA – so much more than just a genome I Pathogenesis I Replication I Clinical virology

PRIZE MEDAL LECTURE

- To be delivered by Nobel-Prize-winning virologist Professor Harald zur Hausen.

KEY DATES

- **MONDAY 14 JANUARY 2013 (NOON)**: abstract submission closes
- **FRIDAY 22 FEBRUARY 2013**: earlybird registration closes

GRANTS AVAILABLE FOR:

- Associate Members who are postgraduate students, retired or technicians
- Qualifying Undergraduate Student Members

Manchester Central

SAVE THE DATES

SGM Autumn Conference 2013, University of Sussex
2–4 September 2013

Symposia

Microbial subversion of the host I Microbial survival in the host I Fungal diseases, diagnostics & drug discovery I Emerging fungal pathogens I Impact of phage I Regulatory phosphate-based molecules I Sustainability of microbiology as a profession

SGM Spring Conference 2014
Arena and Convention Centre Liverpool
14–17 April 2014

Other SGM-sponsored scientific meetings

Recent Independent Virology Researchers' (RIVR) Meeting 3–4 January 2013, Marriott Breadsall Priory, Derby

CRISPR: Evolution, Mechanisms and Infection 17–19 June 2013, University of St Andrews

MICRO SHORTS

Microbes and metabolism

The gut microbiota of women has been shown to change dramatically during the course of pregnancy, and by the third trimester the composition resembles that seen in some inflammatory gut disorders. The work sheds light on the complex relationship between the gut microflora and host metabolism. A Finnish study collected stool samples, diet information and clinical data from 91 pregnant women. The microbiome was more diverse during the first trimester with a profile similar to that for healthy individuals. However, by the third trimester the diversity was generally reduced and the relative abundance of *Proteobacteria*, which are associated with inflammatory conditions such as inflammatory bowel disease, was significantly higher. When the microbiota from the third trimester of pregnancy was transferred into germ-free mice, this induced pregnancy-like metabolic changes. Importantly, this work suggests that the host microbiota impacts host metabolism during pregnancy by promoting the storage of energy in fat tissue, which is beneficial to support growth of the foetus. However, in non-pregnant individuals this increases the risk of type 2 diabetes and is associated with disease states.

Cell *doi:10.1016/j.cell.2012.07.008*

Jessica Blair *University of Birmingham*

JMM

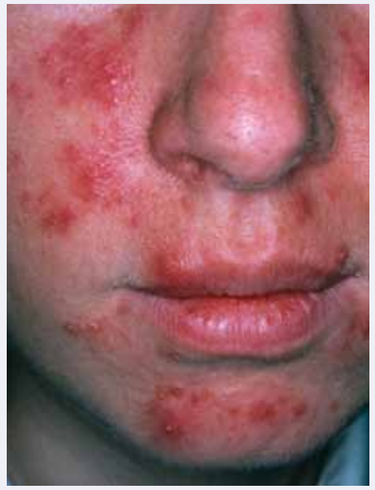
Bacteria 'mite' cause rosacea

Rosacea, a common skin disease, is primarily caused by bacteria, aided by *Demodex folliculorum* mites that live in the skin, according to a new review. The findings should lead to more targeted treatments for the condition. Rosacea, characterised by inflammation and lesions in the central regions of the face, affects nearly 3% of the population and is more common in women than in men. High densities of *Demodex* mites are common in patients suffering from rosacea. *Bacillus oleronius* has been isolated from the gut of *Demodex* mites from rosacea patients. It is speculated that the proteins released by *B. oleronius*, upon death of the mite, stimulate an immune response that triggers rosacea. Further research on the role of these bacteria and *Demodex* mites will help shed light into the pathogenesis of the disease and could lead to novel ways to prevent and control rosacea.

JMM *doi:10.1099/jmm.0.048090-0*

Sruthi Raghavan *Freelance writer*

Rosacea.
CNRI / Science Photo Library



Could bacteria solve our energy needs?

Scientists have shown that the energy bacteria produce while degrading wastewater can be harvested to make electricity. Capturing this source would create a new energy supply and avoid the consumption involved in wastewater treatment, according to recent review of the topic. In the US, 3% of all electrical power is used in wastewater treatment. However, this wastewater also has huge energy potential. New technologies use bacteria to catalyse electrochemical reactions using waste organic matter as a substrate. The most studied electrogenic organisms are *Geobacter* and *Shewanella* species, though many others could also be used. Research is currently taking place to assemble bacterial communities that can produce electricity by degrading the complex mixture of compounds found in wastewater. At the moment, it is cheaper to produce electricity through traditional methods rather than microbial technologies. However, as fossil fuels become more scarce, microbial technologies are likely to prove a viable alternative.

Wastewater.
iStockphoto / Thinkstock

Science *doi:10.1126/science.1217412*

Lena Ciric *University College London*

Super-sensitive biosensor enhances virus detection

A sensor that can detect the smallest known viruses has been created. It works by sending light waves resonating at a specific frequency within a glass sphere; the presence of a virus changes the resonant frequency of the light within the sphere. Researchers from the Polytechnic Institute of New York University called the sensor the Whispering Gallery-Mode Biosensor after the circular gallery in St Paul's Cathedral, where someone whispering near the wall can be heard around the gallery. The sensitivity of the sensor was increased by attaching gold nanoparticles to the glass sphere, enabling detection of minute changes in resonant frequency. The gold sensor meant even the tiny MS2 virus, which is 1% of the mass of the influenza A virus, could be detected. This development holds enormous potential for early identification and treatment of disease.

Applied Physics Letters *doi:10.1063/1.4739473*

Daniel Amund *London Metropolitan University*

Microbiology

Antimicrobial essential oils – not to be sniffed at

Plant-derived essential oils show greater toxicity against pathogenic micro-organisms compared to commensal gut bacteria, according to a new study. The work contributes to the development of essential oils as health-enhancing food additives to treat or prevent colonic microbial imbalances. Researchers from the University of Aberdeen found that the essential oils from cloves, coriander, curcuma and geranium, and their purified chemical components, exhibited different growth-inhibitory effects, depending on their chemical characteristics. Pathogenic gut bacteria such as *Escherichia coli* O157:H7 and *Clostridium difficile* were, in general, more sensitive to the essential oils and their constituents than the commensal strains. The inhibitory effect was shown not to be due to membrane damage. While these results show great promise, further optimisation, including studies using mixed cultures and *in vivo*, is required in order to ensure the protection of beneficial commensal strains.

Microbiology *doi:10.1099/mic.0.061127-0*

Mireille Vankemmelbeke *University of Nottingham*

Coriander.
iStockphoto / Thinkstock

Unlikely commensals: wasps and yeasts

Wasps are an important reservoir and vector of many yeast strains, including *Saccharomyces cerevisiae*, according to a new study. Researchers recognised that yeasts found in nature, such as those associated with grapes, could be readily isolated from their environment during the warmer months. However, where the yeasts resided in the autumn and winter was unclear. The University of Florence research team suspected that wasps may carry yeasts in their gut because they fed on grapes and other fruits during summer. To test their theory, they isolated the microflora from the guts of hornets, wasps and honeybees from different locations in the Italian countryside. Wasps were found to harbour yeast strains during the winter, and actually transmit yeasts to their offspring. This work helps shed light on the natural history of yeasts, which remains poorly understood despite their importance in food and beverage production and molecular biology.

PNAS *doi:10.1073/pnas.1208362109*

Greg Potter *Dalhousie University, Canada*

Wasp feeding on a plum. *Stockbyte / Thinkstock*

JULIAN DAVIES

Antibiotic discovery: then and now

There is much discussion about how we tackle the antibiotic crisis now and in the future, but the story of how we arrived at this point is just as fascinating.

THE PRESENCE of antimicrobial agents has been known since the days of Louis Pasteur – who else? When Pasteur and Joubert described the phenomenon of bacterial antagonism in 1877, they noted that the growth of *Bacillus anthracis* was restricted in the presence of other bacterial strains and commented that such activity might well be of therapeutic value. Somewhat later, in 1928, Papacostas and Gaté described a number of examples of the phenomenon, involving different bacterial genera and species. They presented this phenomenon as antibiosis and even used the word '*antibiotique*'. However, it was not until 1945 that Selman Waksman formalised the name and defined an antibiotic as a '*chemical substance of microbial origin that possesses antibiotic powers*'.

It is now known that many organisms produce chemicals with antibiotic activity and a number of such compounds can be made synthetically. The production of antibiotics and other compounds by microbes was previously considered to be a process of secondary metabolism (usually triggered by signals in later stages of growth and development). However, given the fact that the products are in no way secondary, the preferred description is 'specialised metabolism'. 'Antibiotic' is synonymous with 'antimicrobial' and the two are used interchangeably, especially in the popular press. Most are produced by streptomycetes, but bacilli, pseudomonads and fungi all produce a variety of therapeutically active chemicals. Interestingly, the pyocyanins, products of *Pseudomonas* spp., were used in the late 1800s, and may have been the first antibiotics employed clinically. It is worth noting that some chemicals discovered as antibiotics have had greater value in other medical applications; good examples are cyclosporin and rapamycin (sirolimus) that are active immunosuppressants and have transformed the science of transplantation medicine.

In the late 1930s, the sulfonamides came onto the scene and they proved to be the first revolution in antimicrobial therapy. This genuine target-based therapy (Ehrlich-style) was very successful; even though this class of compounds has a limited spectrum of activity, these drugs were used throughout the Second World War – and still are! The golden age of antibiotic discovery began with the use of penicillin and subsequently streptomycin at the end of the Second World War; penicillin was responsible for saving many lives in the battles following D-Day and in the Japanese campaigns. These two antibiotics were discovered with very primitive, functional screens, the kind that can be done in secondary school classes anywhere nowadays. Of course, the essential discovery process was to isolate, purify and characterise the active compound(s) and show that they are novel, active and non-toxic.

Original laboratory sample of 'M&B 693' (1938), one of the first sulfonamide antibiotics. It was used for treating pneumonia and gangrene.
Wellcome Library, London / Science Museum, London

A critical element in the introduction of antibiotics during the early days of antibiotic discovery was the mobilisation of the pharmaceutical and fermentation industries in the US and, subsequently, in the UK. As more companies started looking for bacteria and fungi capable of producing active antibiotics, the actual discovery process changed little, other than in magnitude. Screening depended on manpower, and chemical identification of potential candidate antibiotics was a slow business using the traditional approaches of natural products research. Nonetheless, by the mid-1940s, in addition to penicillin and its derivatives, the first antibiotic active in the treatment of tuberculosis, streptomycin, was discovered by Albert Schatz in Waksman's laboratory. Subsequent entries into the pharmaceutical arena included chloramphenicol, tetracycline, erythromycin, lincomycin, polymyxin and vancomycin; certainly hundreds of other compounds discovered by Waksman-style screening failed to make the grade because of insolubility, toxicity, instability, serum binding, colour, smell, poor activity spectrum, low yield or some other inadequacy. Screening for compounds was routine and simple, every company isolated many candidates but few made the cut-off.

Albert Schatz (1920–2005) who discovered streptomycin, photographed in 1943.
Special Collections and University Archives, Rutgers University Libraries

> "The future discovery of new antibiotics and other therapeutic agents can now be envisaged as a process involving the identification of biosynthetic pathways for small molecules, and productive expression of the pathways by cloning into heterologous hosts or by metabolic activation."

As physicians throughout the world faced increasing examples of recalcitrant infections due to the development of resistance during treatment, the industry made serious efforts to produce antibiotic derivatives with activity against resistant strains; this became more and more of a losing proposition. Nonetheless, there were notable successes, for example methicillin (now meticillin) and other β-lactamase-resistant penicillins and cephalosporins, and even modified aminoglycosides. However, there was always an Achilles heel in the antibiotic structure and these successes were only temporary.

The development of resistance did not alone lead to the end of the 'golden era' of antibiotics. Regulatory authorities have demanded increasingly strict and extended clinical trials for the protection of the human population (especially after the thalidomide disaster) and the ability to meet all requirements has been difficult. In addition, microbes themselves have shown genetic adaptability in ways not previously anticipated. The first reports of transferable antibiotic resistance in the late 1960s were greeted with disbelief from the scientific and medical community. However, it is now recognised as the major factor in the global spread of resistance and efforts to eliminate or prevent horizontal gene transfer have been totally unsuccessful. Why did the golden era end? It seems as if most of 'Big Pharma' lost interest in antibiotics at the same time. The older antibiotics still worked in most cases and the enormous cost of new antibiotic discovery and arduous clinical trial procedures discouraged new investment when the long-term and profitable illnesses of an aging population needed attention. Production was even discontinued in the Western world; by the 1980s, most antibiotics were being mass-produced in countries like India and China.

In the late 1980s, a number of pharmaceutical companies made attempts to employ novel high-throughput methodologies to develop screening processes enabling the identification of new antibiotic molecules, but most of the efforts came up empty-handed. There was even a belief that all of the accessible structural scaffolds for antibiotics had been uncovered. Industrial antibiotic discovery reached a new low. However, the advent of the genome sequencing era in 1995 with the success of the Venter group in obtaining the complete genome sequences of two bacterial pathogens triggered a new wave of optimism in the industry since it was thought that these sequences would permit the identification of novel, metabolism-based targets. Several industrial groups took this route, but the success rate was low and the products lacked novelty. In addition, the inherent weakness of 'designer' chemical libraries was at fault and the hit rate was very disappointing. This led to additional Big Pharma drop-outs from the field and the onus for antibiotic discovery fell on small biotech companies, most of which lacked the finance and personnel to take advantage of the increasing catalogue of near-complete genome sequences of pathogens. In the 1990s, the only new antibiotics to be introduced were 'rediscoveries' from earlier times. The prospects for antibiotic discovery were not promising.

The event that has brought about a major philosophical change in antibiotic discovery was the complete genome sequencing of *Streptomyces coelicolor*, an antibiotic-producer, not a pathogen. This, the largest bacterial genome to be sequenced at this time (~9.0 Mb), was a real eye-opener since it revealed that *S. coelicolor*, known to produce a small number of pigments and other bioactive molecules, has in fact the genetic capacity to produce more than 20! Suddenly, the claims by pharmaceutical companies about having discovered most of the compounds available became fiction. It became apparent that there are orders of magnitude more antibiotics and other pharmaceutical agents available in nature. Complete genome sequencing studies have revealed that a large number of microbial genera possess many hidden biosynthetic pathways for bioactive molecules: the huge phyla of *Actinobacteria* and *Firmicutes*, and the '*Myxobacteria*', etc. The number is unimagineable. The question is how to exploit this information and obtain the compounds for investigation.

High-throughput metagenomic sequence analysis of microbial populations (microbiomes) from diverse environments has raised awareness that bacteria and other microbes do not live in isolation, but exist in huge interactive communities. These communities employ distributed metabolic processes that are regulated by chemical signalling by bioactive small molecules. This was first made obvious by the discovery of quorum sensing interactions in which the signalling molecule concentration is determined by the size of the bacterial population. Quorum sensing has been identified in many bacterial interactions. As mentioned above, most bacterial genomes possess biosynthetic pathways for a large number of small molecules, some of which have been identified as antibiotics. However, these so-called antibiotics may actually be used in nature as signalling agents. Support for this notion comes from the fact that antibiotics at sub-inhibitory concentrations can act as signalling molecules to regulate transcription in bacteria; at these concentrations, they influence multiple cellular activities. Studies of the mode of action of antibiotics have revealed that their targets include the core functions in the cell: transcription, translation, replication and many aspects of metabolism. There is increasing evidence that sub-inhibitory antibiotics do not inhibit, but modulate these functions. For example, the antibiotic rifampicin, a well-characterised inhibitor of RNA polymerase, actually stimulates the production of specific transcripts at low concentrations. The signalling functions of many of these compounds have been demonstrated in cross-kingdom interactions.

The future discovery of new antibiotics and other therapeutic agents can now be envisaged as a process involving the identification of biosynthetic pathways for small molecules, and productive expression of the pathways by cloning into heterologous hosts or by metabolic activation. Structure determination can always be a problem but newer physical methods and sophisticated instrumentation should provide solutions. The compounds obtained can then be detected, purified and screened using sensitive transcriptional assays.

By exploiting the increasingly rapid and sensitive techniques for genome sequencing and bioinformatic analysis, it will eventually be possible to gain complete access to the parvome (the '-ome' of the small chemical molecules produced by living organisms). This will transform drug discovery and provide constant stimulation for new pharmaceutical developments, especially those employing synthetic biology.

Selman Waksman (1888–1973, centre), working with researchers in his laboratory. *National Cancer Institute / Science Photo Library*

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See Julian present his SGM Prize Medal Lecture 'Molecules, Microbes and Me' on 26 March 2012 at the Society for General Microbiology's Spring Conference 2012 in Dublin at http://bit.ly/Rg75WB

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Accessing the biosynthetic potential of *Actinobacteria*

PAUL A. HOSKISSON

In an era of ever-increasing antibiotic resistance, can bacteria still provide a source of desperately needed novel antimicrobials?

Secondary metabolite droplet on a *Streptomyces* lawn. *Marco Gottelt (Groningen) & Eriko Takano (Manchester)*

THE EMERGENCE of antibiotic-resistant micro-organisms was inevitable as soon as antibiotics were introduced to the vast array of drugs and treatments available to clinicians. Perhaps one surprise was the speed in which the first cases of resistance were observed in pathogens. Soon after, the race to find new antibiotics began in earnest. One source of potential new antibiotics was the *Actinobacteria*, one of the most abundant bacterial phyla on the planet, comprising up to 30% of the bacterial flora in some niches. Within their ranks are important human pathogens such as *Mycobacterium tuberculosis*, the causative agent of tuberculosis, but also the important antibiotic producers such as the *Streptomyces* species. *Streptomyces* is not the only genus that is useful industrially; indeed, many members of the phylum produce molecules that are useful as antibiotics, anticancer agents, antihelminthics or immunomodulators; these are often referred to as secondary metabolites as they are not essential for growth.

The discovery, by Selman Waksman, that the *Actinobacteria* were a good source of secondary metabolites, through the discovery of streptomycin production by *Streptomyces griseus* in 1943, meant that this group subsequently received an enormous amount of attention in order to add to our armoury of drugs. This arms race to find new weapons against resistant pathogens continued from the mid-1940s, through the golden age of antibiotic discovery in the 1960s, yet began to decline in the 1970s and 1980s. This decline in the introduction of new antibiotics was partly due to the rediscovery of the same molecules repeatedly in the same niches (*Actinobacteria* are common inhabitants of soil), and partly through the tightening of drug-licensing regulations, making it harder to bring new drugs to the market. However, with the need for new anti-infective drugs probably greater than ever, we need to be more cunning in our ability to discover and bring new antibiotics to the clinic.

THE POWER OF SEQUENCING

There are few, if any, areas of biology that have remained untouched by the power of whole-genome sequencing. The emergence of rapid, next-generation and third-generation sequencing technologies (454, Illumina, PacBio and Ion Torrent) has further advanced this progress at a pace, enabling rapid and cost-effective genome sequencing on the bench of any molecular biology laboratory. The first complete *Streptomyces* genome was published in 2002, through a collaboration between Professor Sir David Hopwood's group at the John Innes Centre and the Wellcome Sanger Centre. Thereafter, the floodgates opened and there are over 100 *Streptomyces* genome projects listed currently on GOLD (www.genomesonline.org). One of the most surprising findings to emerge from all these genome sequences is the biosynthetic potential of these organisms. We have known for many years that most *Streptomyces* produce more than one secondary metabolite; however, studying the genome sequences has shown us that these organisms have the potential to produce many more, potentially useful metabolites. The model species, *Streptomyces coelicolor* A3(2), was known to produce three secondary metabolites – examining the genome sequence raised this number to over 20! This potential biosynthetic capability has been a recurring theme as each genome sequence is completed and the sequence-gazing begins. They are often referred to as silent gene clusters (the genes encoding secondary metabolites are often found together in clusters in the genome) as the

products have yet to be 'seen' in cultures and are probably not expressed under the culture conditions that have been studied.

GIVING A VOICE TO THE SILENT MAJORITY

These previously unknown secondary metabolite gene clusters provide us with a challenge – to activate them and study the potential utility of their products. A range of approaches has been taken to study these clusters, including cloning them and expressing them in another *Streptomyces* species. This may enable the global regulatory processes controlling their expression in their native producer to be circumvented. Simple disruption of the pathway-specific regulators, which are easily identified within secondary metabolite clusters by bioinformatics, has been shown to result in activation of the genes within a cluster. Other approaches have included the manipulation of antibiotic genes through the use of short DNA sequences that interfere with regulatory proteins, thus ameliorating the effects of proteins that repress gene expression. The use of various stress and nutritional conditions has also yielded good results in terms of manipulating antibiotic production, such as the use of common soil carbon sources such as *N*-acetylglucosamine to activate expression of previously unobserved metabolites. This enhancing of secondary metabolism through the manipulation of cellular metabolism has great potential for awakening these silent clusters.

Recently there have been significant advances in the cloning of large DNA fragments directly from the environment. The gene clusters that encode secondary metabolites are generally in the region of 25–60 kbp in length; therefore, the ability to clone these genes from environmental samples is now a real possibility, often referred to as the metagenomic approach. This allows us to access novel secondary metabolites directly from the environment, without the need to culture the producing organism. These genes can then be expressed in a suitable heterologous host bacterial strain, of which there are many, including specially engineered strains of *Streptomyces* that don't produce the majority of their own natural metabolites, and so are excellent producers of heterologous metabolites. One of the keys to identifying clusters using this approach is to explore previously neglected environmental niches, such as the deep-sea environment, hyper-arid deserts and Antarctica, all of which are yielding potentially interesting new antibiotics. The limitation of these approaches is the intensive screening required to identify biological activity in the cloned sequences.

SYNTHETIC BIOLOGY APPROACHES TO NEW ANTIBIOTICS

One of the most exciting approaches to emerge recently is the potential to apply synthetic biology to antibiotic production, discovery and manipulation. Synthetic biology can be thought of as the repurposing or redesign of biological systems for novel applications. The clustering of secondary metabolite genes offers a big advantage to the manipulation of their function, expression levels and production. Whilst synthetic biology is one of the current 'buzz' words in biology, this manipulation of antibiotic biosynthetic clusters is not particularly new. Since the mid-1980s, various groups interested in *Streptomyces* have been trying to make so-called 'non-natural natural products' using an approach called combinatorial biosynthesis (using genetic engineering to modify biosynthetic pathways to make new compounds). The ability to manipulate these clusters using molecular biology offers several advantages, not only in terms of generating novel activities, but also improving the pharmacokinetics of drugs, and reducing toxicity.

One group of secondary metabolites that has been amenable to combinatorial biosynthesis and has received lots of attention is the polyketides. Polyketides are synthesised by large multimodular enzymes that link simple precursors, such as acetyl-CoA or malonyl-CoA, in an iterative nature, growing chains that are tethered to an acyl carrier module on the enzyme. Manipulation of these multimodular enzymes then allows for alteration of the metabolite chain. Several methods have been used, such as those where simple gene disruptions can alter one of the chemical reactions during biosynthesis, resulting in longer or shorter chains, or without additional chemical decorations. Interestingly, one approach that has yielded amazing results is the formation of hybrid polyketides simply by transferring polyketide clusters into organisms producing related molecules. This allows the machinery from one cluster to modify the product in another in a very simple manner (see Fig. 1).

> "There are limitations to the modifications that certain chemical scaffolds are amenable to; however, we can envisage the very first, truly synthetic antibiotic biosynthetic gene cluster in the not-too-distant future."

TOWARDS A TRULY SYNTHETIC BIOLOGY OF ANTIBIOTICS

The relatively simple experiments that have been carried out to date have wide-ranging implications; however, now we can couple these with the advances in molecular biology such as assembly of large DNA fragments, ligation-free cloning, and the advent of 'BioBrick' technology (www.biobricks.org) to create a truly synthetic biology for antibiotics. The multitude of secondary metabolite biosynthetic clusters available in the sequence databases means that we can assemble any enzyme simply from short oligonucleotides, introduce it into any biosynthetic cluster and examine the potential to alter the characteristics of the metabolite produced.

Of course, there are limitations to the modifications that certain chemical scaffolds are amenable to; however, we can envisage the very first, truly synthetic antibiotic biosynthetic gene cluster in the not-too-distant future. The assembly could be undertaken using BioBrick-type technology where each genetic unit is pieced together like *LEGO* bricks until a complete cluster is assembled. There is still a lot of work to undertake, as with any synthetic biology project. We need to understand and develop good regulatory sequences and promoters, and efficient ribosome-binding sites for manipulating expression levels and the overall logistics of piecing these together. Yet all of these approaches are tantalisingly within our grasp and will enable us to carry out bio-inspired chemistry synthetically in a bacterium in the near future.

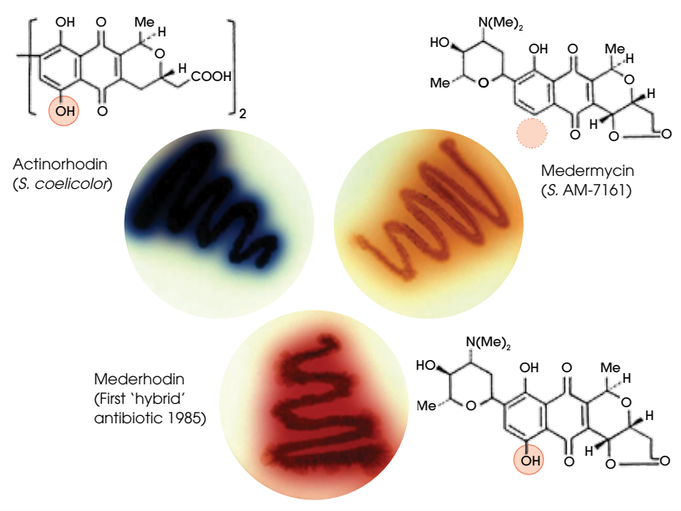

Fig. 1. **Hybrid polyketide biosynthesis. *Streptomyces* sp. AM-7161, making the brown-pigmented medermycin (top right) and *S. coelicolor* making the blue-pigmented actinorhodin (top left). The actinorhodin biosynthetic cluster was introduced into *Streptomyces* sp. AM-7161, creating the hybrid polyketide, which was called mederrhodin (bottom), which differed from medermycin in the addition of an -OH group.** *David Hopwood*

ACKNOWLEDGEMENTS

Thanks to Professor Sir David Hopwood for the use of the picture in Fig. 1.

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Waging war on fungi – the unknown superbugs

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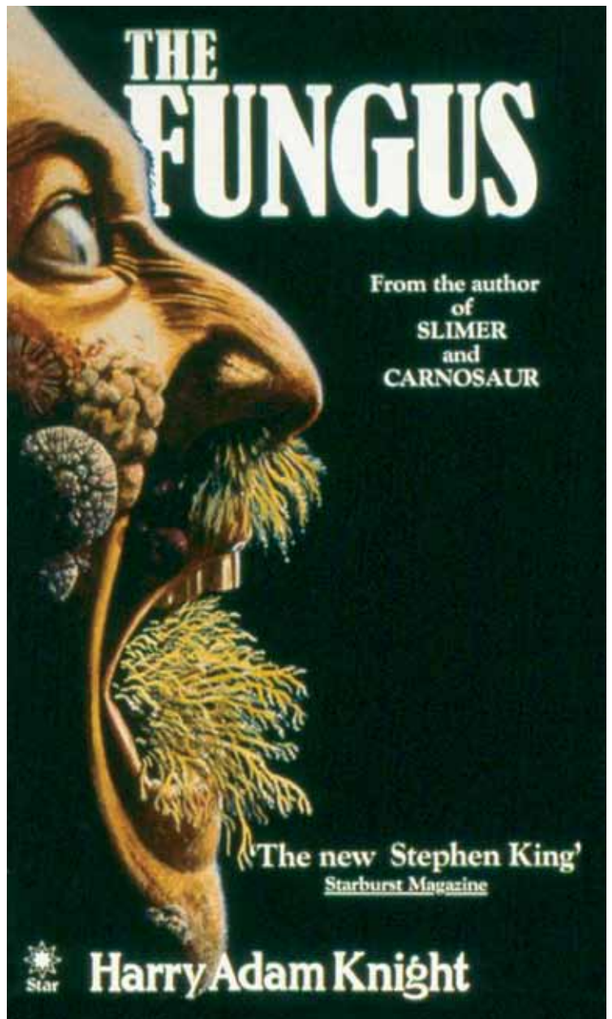
Despite the alarming number of people (not to mention crops and animals) killed by serious fungal infections every year, funding for medical mycology research is disproportionately low. However, the researchers are starting to fight back …



The Fungus, by Harry Adam Knight (published by Star Books), speculates on the fictitious ravages of medical mycology. *Used by permission of The Random House Group Ltd*

THE PUBLIC HAVE COME to recognise infectious diseases caused by bacteria such as MRSA, *C. difficile*, *E. coli* and *Legionella*, viruses (e.g. common cold, influenza, AIDS) and parasites (e.g. malaria, leishmaniasis, sleeping sickness) as household names, while those caused by fungal pathogens such as *Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis* and others, remain unknown, unfeared and often undiagnosed. However, each year fungi are responsible for around 1.5 million deaths and cost $12 billion to treat worldwide. In addition, fungal pandemics threaten ecologically important groups of animals and staple crops in a way that threatens global biodiversity and food security. Why is it, therefore, that so little emphasis is placed on fungal pathogenicity in general, and in particular, only about 2–3% of the infectious disease research budget is currently devoted to medical mycology in the UK, USA and Europe?

The reason is clearly not due to size of the clinical burden – which is impressive. Let's consider some more statistics and fungal factoids. Fungal skin, hair and nail infections are an itch that affects a quarter of the world's population. These common infections are caused by dermatophytes and give rise to several well-known conditions, such as athlete's foot (tinea pedis) and ringworm of the scalp (tinea capitis). Mucosal infections of the mouth and genitals are also common. For example, it is estimated that 75 million women experience recurrent episodes of vulvovaginal candidiasis (or thrush) annually. Oral thrush is more likely to occur in babies, denture wearers and individuals using inhaled corticosteroids for asthma. Fungal allergy is also common, but robust epidemiological statistics elude us. Although uncomfortable and distressing to the individual, these infections and allergies are not often life-threatening and are generally treatable.

Of greater concern are invasive fungal infections which have much lower incidence rates than superficial infections but have alarmingly high mortality rates, despite treatment with antifungal drugs. Patients with compromised immune systems (associated with cancer, trauma and HIV) and those undergoing invasive clinical procedures (stem cell, bone and organ transplants) are particularly susceptible to these invasive, life-threatening infections, and mortality rates mostly range from 30 to 80% depending on the invading pathogen and the underlying condition. Current figures for incidence and mortality rates are likely to be underestimated due to inadequate epidemiological data, misdiagnosis because of unreliable diagnostics and a lack of global reporting in areas of the world with high endemic disease problems. Incredibly, only one fungal disease (coccidioidomycosis) holds the status of a notifiable disease at the Centers for Disease Control and Prevention (USA).

While there are over 600 species of fungi that can infect humans to cause

> It is barely appreciated that the burden of cryptococcal disease in sub-Saharan Africa is so high that it accounts for more deaths than malaria and AIDS-associated tuberculosis.

a variety of diseases, over 90% of all fungus-related deaths are due to species belonging to only four genera; *Candida*, *Cryptococcus*, *Aspergillus* and *Pneumocystis*.

Candida species are the fourth most common cause of hospital-derived bloodstream infections in the developed world. The estimated annual global incidence of candidiasis, a bloodstream infection caused by *Candida albicans*, is 400,000 cases per year. Approximated mortality rates for candidiasis are very high, ranging between 46 and 75%.

There are over one million cases of *Cryptococcus* infections per year worldwide. The majority of cases present with meningoencephalitis (meningitis). AIDS patients are particularly susceptible and mortality rates among this group vary significantly, depending on geographical location, with 15–20% in the USA and 55–70% in sub-Saharan Africa and Latin America. It is barely appreciated that the burden of cryptococcal disease in sub-Saharan Africa is so high that it accounts for more deaths than malaria and AIDS-associated tuberculosis.

Aspergillus-related infections mainly arise in the lungs (e.g. chronic obstructive aspergillosis) and can be life-threatening to individuals with underlying conditions like tuberculosis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. Current estimates for invasive aspergillosis show greater than 200,000 cases per year worldwide and there may be a further 450,000 deaths per annum due to COPD. Despite early diagnosis and treatment, this invasive disease carries an overall 50% mortality rate and, if undiagnosed, the outcome is almost certainly fatal. In addition, *Aspergillus fumigatus* is also classified as an aeroallergen and is linked to the development of severe asthma with fungal sensitisation (SAFS), which is thought to affect up to 13 million adults worldwide.

Pneumocystis gives rise to pneumonia-like symptoms in immunocompromised individuals. It is the number one most serious infection in people with advanced HIV. Calculations using existing data estimate that the worldwide incidence of *Pneumocystis* infection is at least 400,000 cases every year with mortality rates varying between 20 and 80%.

Regardless of the global health and economic burden, fungal diseases remain understudied and they remain the unknown superbugs. There is a clear need now to seriously advance our understanding of fungal infection and immunity. Other issues that require urgent attention include the need to invest in the development of safer and more effective antifungal drugs and fast, reliable diagnostics. Again, it is salutary that, in terms of preventing fungal infections, there are currently no approved human vaccines for any fungal pathogen, and this situation needs immediate attention.

In response to a call for urgent action to redress the balance in infectious disease research, the Wellcome Trust has recently awarded a £5 million Strategic Award (WTSA) to the University of Aberdeen to lead a major pan-UK consortium in Medical Mycology and Fungal Immunology, which will tackle some of the major problems in this important but neglected field of medicine. This pan-UK consortium has three objectives: (i) to provide training for a new generation of medical mycologists in areas of the world with high endemic diseases and little specialist expertise; (ii) to build clinical academic capacity in the UK; and (iii) to foster and promote cross-disciplinary research excellence that takes advantage of the highly active, but dispersed communities of medical mycologists in the UK. The focus of the research will be to promote studies that will develop new chemotherapies, immunotherapies and diagnostics through an understanding of fundamental aspects of medical mycology and fungal immunology. The resources that have been funded will support basic science and clinical PhD studentships as well as a limited number of postdoctoral fellowships. Invitations for projects for these posts are available to academic and clinical staff at any UK university. (For information about the funding opportunities supported through this WTSA, please see **www.abdn.ac.uk/mmfi**)

Mycologists have begun to fight back, but the war has only just begun. High-quality research around the world is beginning to make inroads to these terrible human diseases, and initiatives like the WTSA are enabling the linking of arms and assembly of forces for a coordinated attack on a too-long neglected group of pathogens.

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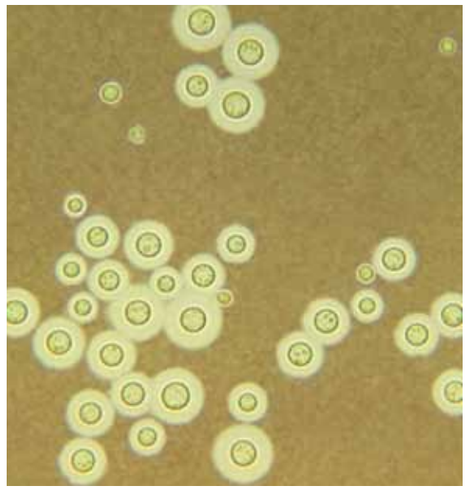


***Candida albicans* (left, SEM), *Aspergillus fumigatus* (centre, SEM) and *Cryptococcus neoformans* (right, India ink stain) – three of the four biggest fungal killers worldwide.** *N. Gow (C.a.) Eye of Science / Science Photo Library (A.f.) – CDC/ Dr Leanor Haley (C.n.)*

Enzybiotics and phages: safe alternatives to antibiotics in the control of food safety

PATRICIA VEIGA-CRESPO & TOMAS G. VILLA

Chickens on a fence. *Digital Vision / Thinkstock*

The concept of treating bacterial infections with phage is not new – indeed it pre-dates the antibiotic era. Can this be used to eliminate the use of antibiotics in animal feed?

RECENTLY, the US Food & Drug Administration (FDA) issued an order prohibiting the use of cephalosporin drugs in cattle, swine, chickens and turkeys (docket no. FDA-2008-N-0326; www.regulations.gov). Cephalosporin-based antibiotics are important in treating human diseases such as pneumonia caused by *Streptococcus pneumoniae*, or skin and soft-tissue infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. These drugs are also effective against other bacteria, such as *Acinetobacter calcoaceticus*, *Bacteroides fragilis*, *Enterobacter agglomerans*, *Escherichia coli*, *Haemophilus influenzae* (including β-lactamase-producing strains), *Klebsiella oxytoca*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

ANTIBIOTIC RESISTANCE

The FDA is concerned about the use of antibiotics in food-producing livestock because they are likely to contribute to the generation of resistant strains of certain bacterial pathogens, thus increasing the risk of antibiotic-resistant infections in humans. In the case of cephalosporins, the risk of microbiological or toxicological undesirable side effects in food-producing animals still remains unknown. But it is generally assumed that adding antibiotics to animal food in order to increase food production may threaten public health and should be discontinued. When the cephalosporin prohibition finally takes effect, the drug will join others, such as chloramphenicol, dimetridazole, furazolidone, nitrofurazone and sulfonamide derivatives, formerly used in the treatment of lactating cattle.

Bacterial antibiotic resistance can be acquired by two mechanisms: (i) as the result of genetic events causing variations in the bacterial genome; or (ii) by horizontal gene transfer among bacteria.

The fight against antimicrobial resistance has become a great challenge to our civilisation and involves a wide range of experts from different echelons of society and from all over the world. In agriculture, for example, the FDA, via the National Antimicrobial Resistance Monitoring System (NARMS), is charged with the responsibility of investigating resistance trends in food-borne bacteria, assessing antimicrobial resistance risks for

new antimicrobial drugs, and promoting the judicious use of medically important antimicrobials approved for use in food-producing animals.

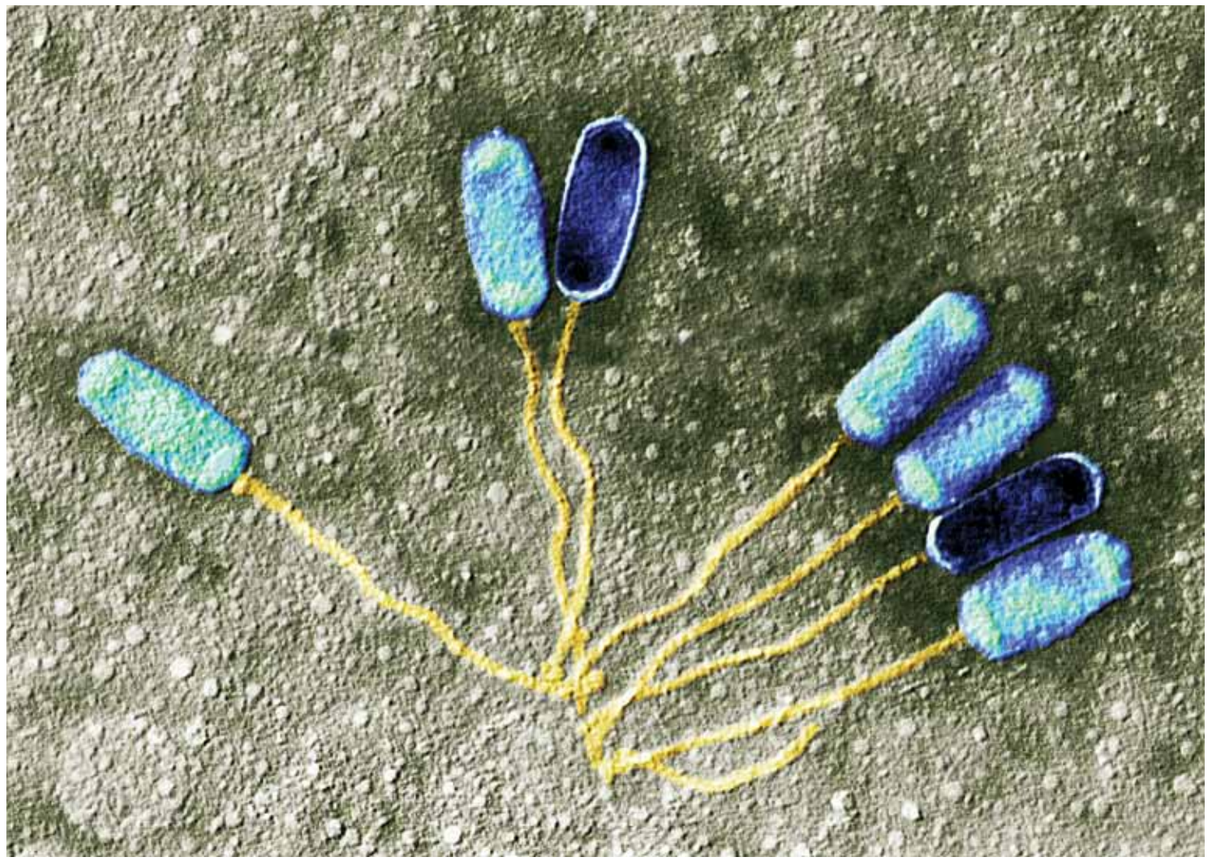
The increase in antimicrobial resistance rates seen during the last few decades is likely to be the result of misuse and overuse of antibiotics; new resistant bacterial strains have emerged and, therefore, the battery of chemotherapeutical drugs available to treat disease has dwindled. This has resulted in an enormous worldwide health care problem, in terms of declining public health and spiralling health care costs. The World Health Organization (WHO) defined the appropriate use of antibiotics as '*the cost-effective use of antibiotics, which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antibiotic resistance*'.

Changes within the pharmaceutical industry may be contributing to the pipeline of new antimicrobials drying up; in fact, the major pharmaceutical companies have practically stopped research leading to the development of new antibiotic drugs. One of the reasons for this cessation is the reduced market profits for antimicrobials, as compared to those generated by other drugs, such as those targeting chronic diseases. In 2000, amoxicillin-clavulanic acid was the only antibiotic in the top 20 prescription drugs. Therefore, the situation needs to be addressed.

BACTERIOPHAGE

Bacteriophages are the most abundant and diverse biological agents on the planet and have been detected in virtually all environments. They were discovered in the early 20th Century and have been applied in the control of bacterial diseases. However, the discovery of antibiotics reduced the interest in bacteriophages as therapeutics. But the increase in antibiotic resistance has now resulted in a resurgence of interest in bacteriophages. The potential of bacteriophages as therapeutic agents was first evaluated in fields such as aquaculture, biocontrol in agriculture and in veterinary medicine. The success of phage therapy for the treatment of septicaemia and meningitis in chickens and calves, or the possibility of using bacteriophages as biocontrol agents to reduce *Salmonella* in poultry products has been well documented. Phages have also been proposed as alternatives to antibiotic sprays to control bacterial infections in high-value crops.

> " As for the undesirable side effects of enzybiotics, they have been scarcely reported, and they have the additional advantage that their immunogenic abilities are quite weak. "



Bacteriophage virions. *Eye of Science / Science Photo Library*

Advances in molecular biology have allowed researchers to focus on two main aspects of bacteriophage-based therapies: (i) administration of whole bacteriophages; and (ii) administration of phage-lytic enzymes known as enzybiotics. In fact, the term enzybiotic is a wider term that refers to those enzymes, independent of their origin, that are able to act as antibacterial or antifungal agents.

They are used as food additives and preservatives, for example in the production of cheese and wine; in medical applications, such as eye drops; and in toothpaste, etc. The FDA has approved the use of bacteriophages to control *Listeria monocytogenes* in cheese, thus classifying them as 'GRAS' (generally recognised as safe) in 2006 (notice no. GRN 000198; www.fda.gov). Additionally, in 2007, the status of GRAS was extended to bacteriophage use on all food products (notice no. GRN 000218; www.fda.gov).

As for any undesirable side effects of enzybiotics, they have been scarcely reported, and they have the additional advantage that their immunogenic properties are weak. Despite the fact that further investigation on the methods for their administration, half-life and effectiveness is still required, enzybiotics constitute a clear and safe alternative to antibiotics as food control agents.

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HELGE B. BODE

Drugs from bugs that kill bugs

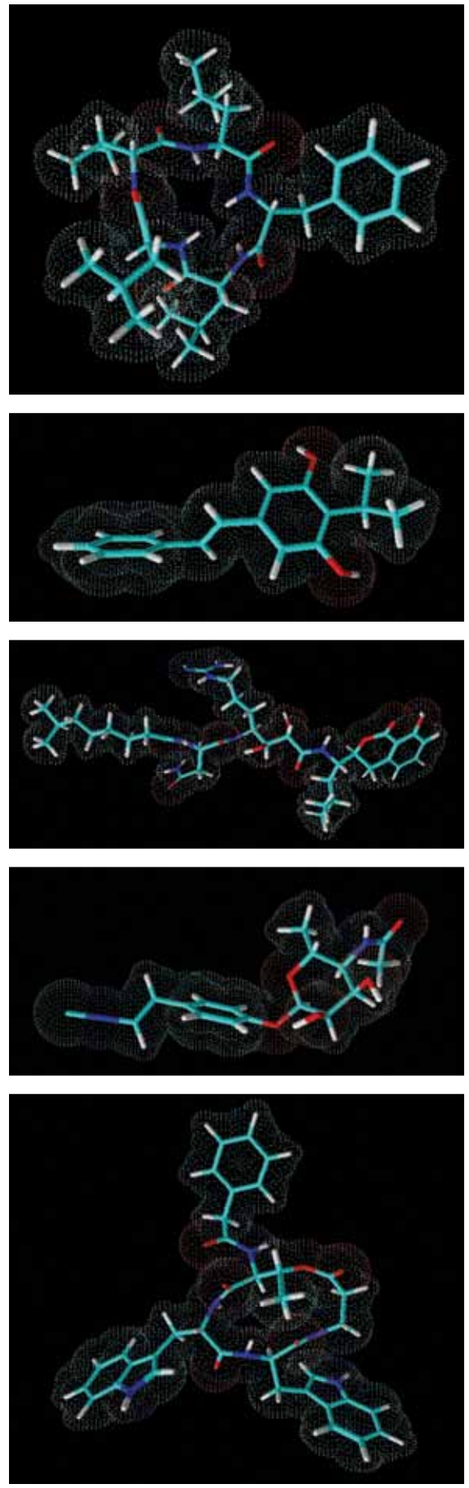
It isn't just soil-dwelling actinomycetes that may hold the key to new antimicrobial compounds. Insect-pathogenic bacteria also produce a host of bioactive compounds – and what's more, they are easy to analyse *in vivo*.

NATURAL PRODUCTS from microbes and plants have been used in human medicine for thousands of years. During the last 60 years they have been especially useful as antibiotics and anti-cancer compounds. Most low-molecular-mass compounds used clinically are in fact natural products, natural product derivatives or have been inspired by natural products. However, the current situation where we have antibiotics to treat many bacterial infections is likely to change rapidly in the next decade or two due to increasing resistance and the emergence of not only multi-, but pan-resistant human pathogens. At the same time, pharmaceutical companies have stepped back from antibiotic research due to high development costs and have concentrated mostly on drugs for chronic diseases.

This dramatic situation in the clinic contrasts with the enormous possibilities of modern science. Next-generation sequencing allows cheap and rapid access to biosynthesis gene clusters in bacteria and fungi, which can be manipulated very efficiently in the original host using genetic tools, or expressed heterologously in more accessible model organisms, such as *Escherichia coli*, *Bacillus* or optimised *Streptomyces* hosts. Additionally, analytical methods, like mass spectrometry, allow the rapid detection and structural elucidation of novel natural products or their derivatives. The development of these tools has already led to the revitalisation of academic natural product research.

PHOTORHABDUS AND *XENORHABDUS* ARE POTENT NATURAL-PRODUCT-PRODUCERS

Detailed analysis of well-known antibiotic producers like *Streptomyces* has shown that their potential to produce novel compounds is still enormous. In addition, it has been shown over the last few years that several other bacterial phyla are in fact promising natural-product-producers. Five years ago, we started to analyse bacteria of the genera *Photorhabdus* and *Xenorhabdus* for their ability to produce natural products, as earlier work had revealed the presence of compound classes unique to these bacteria. *Photorhabdus* and *Xenorhabdus* belong to the *Enterobacteriaceae* and live in symbiosis with nematodes of the genera *Heterorhabditis* and *Steinernema*, respectively. Both bacterium and nematode form an entomopathogenic complex that can infect and kill several soil-dwelling insect larvae and therefore this complex can be used industrially for pest control in organic farming. The nematode can be regarded as the carrier for the bacteria, setting them free once inside the insect, and the bacteria essentially function as the warhead that kills the insects. Several protein toxins are major players in carrying out their deadly job; there are also a number of low-molecular-mass natural products with insecticidal activity that have also been isolated from these bacteria. Another peculiarity of *Photorhabdus* is its bioluminescence, which makes it unique among terrestrial bacteria, and it is already an established tool in modern molecular biology, although its true biological function is still not understood.



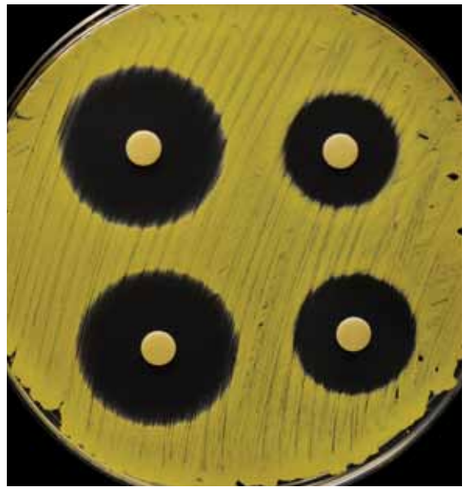
GameXPeptide A, a cyclic pentapeptide from *Photorhabdus*

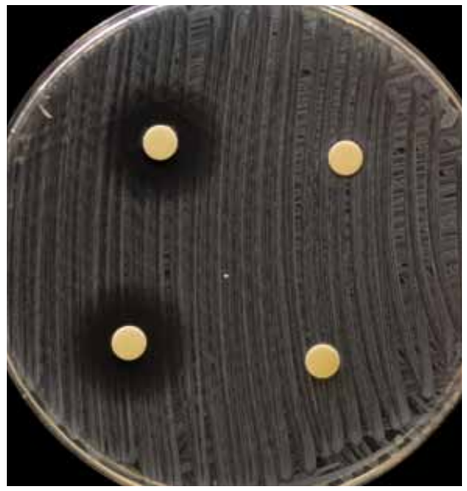
Isopropylstilbene from *Photorhabdus* required for *Heterorhabditis* development. *Photorhabdus* is the only non-plant organism able to produce stilbenes.

Prexenocoumacin C from *Xenorhabdus nematophila*. Prexenocoumacins are inactive prodrugs of the potent antibiotic xenocoumacin-1, which result from cleavage by a specific peptidase.

Rhabduscin produced by *Xenorhabdus* and *Photorhabdus* that inhibits phenoloxidase, which is part of the insect immune system.

Xenematide from *Xenorhabdus nematophila*, an insecticidal depsipeptide.
H.B. Bode





Top left **Larvae of the Greater waxmoth (*Galleria mellonella*) infected with *Photorhabdus* showing the typical bioluminescence. *G. mellonella* is used as a model for bacterial infections.** *H.B. Bode*

Bottom left **Tobacco hornworm (*Manduca sexta*) caterpillar used as a model for bacterial infections.** *H.B. Bode*

Top right **Inhibition zones of compounds from *Xenorhabdus* against *Micrococcus luteus*.** *H.B. Bode*

Bottom right **Inhibition zones of compounds from *Xenorhabdus* against *E. coli*.** *H.B. Bode*

During the course of the EC-funded project 'Genomic approaches to metabolite exploitation from *Xenorhabdus/Photorhabdus*' (GameXP) with partners from the UK (Sharon Peacock, Cambridge; Nick Waterfield, Bath; Richard ffrench-Constant, Exeter), Thailand (Narisara Chantratita, Bangkok), Vietnam (Long Phan Ke, Hanoi) and Germany (Vera Siegmund, Saarbrücken), the chemical diversity of these bacteria was investigated and exploited. More than 200 different bacterial strains were isolated from nematode-infected insects obtained from soil samples (some together with their associated nematodes) and the bacterial strains were analysed using mass spectrometry. Using bioinformatics, over 500 novel compounds have been identified in these bacteria and more than 150 compounds have been isolated and/or synthesised. These compounds range from simple amino acid derivatives like phenylalanine-derived cinnamic acid or simple amides to very large peptides with a molecular mass greater than 1,800 Da. All compounds have been tested against different insects or insect cells, pathogenic bacteria and parasites such as *Leishmania* (leishmaniasis), *Trypanosoma* (sleeping sickness and Chagas disease) or *Plasmodium* (malaria). Different insecticidal and antibiotic compounds have been identified and, more surprisingly, a high proportion of compounds showed activity against the human parasites tested, and some of these are being analysed in detail using *in vivo* models.

Another goal of GameXP was to improve the production of these bioactive compounds and to increase the chemical diversity. As the regulation of the promoters that drive the expression of these compounds is often not understood, these promoters have been exchanged with strong constitutive or inducible promoters, enabling 'on demand' and high-titre production of selected compounds. With the genomes of several chemically diverse strains in hand and several biosynthesis gene clusters responsible for the production of typical natural products like peptides and polyketides already identified, the promoter exchange approach can now be applied to several strains.

> "The high degree of bioactive compounds in general may be the result of the specific ecological niche these bacteria inhabit."

The high degree of bioactive compounds in general may be the result of the specific ecological niche these bacteria inhabit. Being nematode symbionts they must be able to switch between a mutualistic (towards the nematode host) and a pathogenic (towards the insect prey) growth phase; this may require the production of specific small-molecule effectors, signals or toxins. Additionally, they have to protect the dead insect from food competitors, such as soil-dwelling bacteria, fungi and amoebae. Thus, the biochemical similarity between amoeba and human parasites, such as *Plasmodium*, may be the reason for the bioactivities observed.

One major question is how do the bacteria know where they are and what compounds are to be produced in their given environment? The group of Jon Clardy in Harvard has shown that insect blood might trigger the production of some (insecticidal?) natural products. Further triggers are likely to be discovered in the future as these bacteria contain a variety of different sensor systems that might be involved in integrating different environmental cues.

FINDING THE TRUE FUNCTION OF NATURAL PRODUCTS

Another advantage of these bacteria is that the real function of natural products can be studied. Although natural products are indeed important therapeutics, the function and regulation mechanisms leading to their production are mostly unknown. It is clear that bacteria in general do not produce these compounds for the purpose of selling them in a pharmacy! To analyse the natural function of compounds in established producers such as *Streptomyces* or *Bacillus* is more challenging than in *Photorhabdus* or *Xenorhabdus*, as we know only a fraction of their possible interaction partners in their natural environment, the soil. *Photorhabdus* and *Xenorhabdus* can be grown in the lab alone or together with their interaction partners (nematodes, insects or food competitors), allowing the analysis of all possible growth phases of these bacteria using analytical and molecular biology methods. It is evident that some of these natural products must play an important role in mediating these complex interactions from their conservation in several distantly related bacterial strains.

In summary, GameXP has placed *Xenorhabdus* and *Photorhabdus* in the company of other well-known natural-product-producers like *Streptomyces*, *Bacillus* and myxobacteria. Although their compounds still have much to prove in terms of potency as clinical antibiotics or anti-cancer compounds, their potential for therapeutic use is very high.

ACKNOWLEDGEMENTS

The author is grateful to the GameXP team and all members of his group for their enthusiasm and fun during recent years. The work was supported by the EC's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 223328, the German Research Council (DFG) and the LOEWE excellence program Insect Biotechnology.

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Antibiotics in action

Virtually everybody at some point in their life has been prescribed antibiotics by their doctor. These drugs form one of our mainstays in health care against infectious diseases along with vaccination. Interestingly, almost all of these drugs are natural products made by micro-organisms to help them compete in the natural environment. Here, we try to answer some of the most common questions regarding antibiotics.

WHAT ARE ANTIBIOTICS?

Antibiotics are usually small chemical molecules that micro-organisms make and secrete into the environment where they can have an effect on other organisms. Antibiotics belong to many different chemical classes and have a wide range of targets within the cell. They range from small-molecular-mass compounds such as the phenolic antibiotic chloramphenicol, which is made by *Streptomyces venezuelae*, and still commonly used to treat eye infections like conjunctivitis (although all the chloramphenicol used today is chemically synthesised as it is cheaper than *S. venezuelae* fermentation), through to the large macrolide compound erythromycin made by *Saccharopolyspora erythraea*, used to treat respiratory infections. Small peptide antibiotics (e.g. colistins and lantibiotics) have come to prominence in the last few years. In fact one lantibiotic, nisin, is widely used as a food additive.

WHY DO MICRO-ORGANISMS MAKE THEM?

The exact function of antibiotics in the natural environment is a source of much debate. Traditional views have been that they were produced as chemical weapons to kill competitor micro-organisms and provide an evolutionary advantage in highly competitive environments such as soil. This view is changing and it is clear that many compounds only have antibiotic activity at relatively (and artificially) high concentrations. It is these high levels that are used in the clinic to treat infections, but in the natural environment they are present at much lower concentrations and are likely to have signalling roles, either within a species or across species. Interestingly, antibiotics fall into a wider group of molecules produced by micro-organisms, named 'secondary metabolites'. They are so named because they are not essential (i.e. they are secondary) for growth of the producing organism, and it may be that large-scale production is only observed under laboratory conditions. Moreover, many of the organisms that produce antibiotics also produce other secondary metabolites that affect the growth of other kinds of cells, such as cancer cells, or modulate the immune response, or even kill fungi, parasites and worms. So with such a diversity of activities it seems most likely that the response we observe in the lab, and the clinic, is an artefact of using such antibiotics at higher concentrations than they would occur in nature. That said, they are very useful for human health and it is a good thing that they affect biological processes this way! In fact it has been estimated that the introduction of antibiotics led to an 8-year increase in human life expectancy.

WHAT KINDS OF MICRO-ORGANISM MAKE ANTIBIOTICS?

Many different types of micro-organism can produce antibiotics – indeed many species make several different secondary metabolites depending on the growth conditions or at a different stage of their lifecycle. The majority of antibiotics used in medicine are natural products that are made by large-scale industrial fermentation processes. The best-known antibiotic, and the first to be discovered, is penicillin, made by the fungal genus *Penicillium* and some of its relatives, but the undoubted kings of antibiotic production are bacteria. In particular, the *Actinobacteria* (a large and abundant bacterial phylum accounting for almost 30% of all bacterial species) with genera such as *Streptomyces*, *Amycolatopsis*, *Saccharopolyspora* and *Micromonospora* producing a multitude of clinically important antibiotics. Another group of bacteria, the myxococci have more recently revealed themselves as a good source of potentially useful antibiotics.

Antibiotics.
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Generally the micro-organisms that are prolific producers tend to come from highly competitive environments where they may interact with a range of other organisms. Soil has traditionally been a good hunting ground for finding antibiotic-producing micro-organisms, and this has been extended recently to looking in unusual soils from extreme environments such as from permafrost areas and hyper-arid soils from deserts. Deep-sea marine sediment has yielded many interesting compounds in recent years, with one actinobacterium, *Salinispora*, producing several useful antibiotics and anti-cancer drugs.

WHY DO WE SEE RESISTANCE?

Resistance to antibiotics is not really a surprise because bacteria that make antibiotics have to be resistant to them to avoid killing themselves! The resistance genes encoded by antibiotic-producing bacteria can spread to disease-causing bacteria under evolutionary selective pressures, e.g. exposing pathogenic bacteria to antibiotics. There are lots of ways that micro-organisms can avoid being killed by antibiotics and these include altering the antibiotic to prevent its action (such as phosphorylation, glycosylation, adenylation, degradation), altering the target of the antibiotic (such as altering ribosomes, remodelling their cell wall) so the antibiotic cannot bind to its target, or by efflux, essentially ejecting the compound from the cell. Many of these mechanisms are used by the producing bacteria to avoid suicide and they become important when the same resistance arises in pathogenic bacteria. This can arise through spontaneous mutations (a minor route) but more commonly by horizontal gene transfer, a process whereby pathogens can acquire resistance genes from antibiotic-producing bacteria in the environment. A good example is vancomycin that is used as the drug of last resort for treating meticillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin and related glycopeptide antibiotics are made by actinobacteria that live in the soil, but over a period of 45 years the five core resistance genes have spread from *Streptomyces* to MRSA to give vancomycin-resistant MRSA (VRSA), a new superbug resistant to almost all known antibiotics.

HOW CAN WE PREVENT THE SPREAD OF RESISTANCE?

We know that resistance to every antibiotic is present in the environment and can potentially be transferred from one strain of bacterium to another. However, we can significantly slow this process down and avoid the spread of resistance simply by using antibiotics responsibly, i.e. use them exactly as prescribed by the doctor, always finish the antibiotic course even when you are feeling better, and practice good basic hygiene such as washing your hands regularly and covering your nose and mouth with a tissue whenever you sneeze or cough. These are very simple but effective ways of stopping the spread of resistance and infectious diseases.

The discovery of the first natural product antibiotic, penicillin, in 1928 triggered a golden age of antibiotic discovery that revolutionised medicine. In addition to treating infections and cancers, natural products have revolutionised surgery and made organ transplantation possible. Despite this, very few new antibiotics have made it to the clinic since the 1980s and, with multidrug-resistant infections on the increase, we are fast approaching a new age without antibiotics. This imminent crisis has spurred academics and big pharmaceutical companies into action, and with the advent of genome sequencing and many other technological advances since the so-called golden age, the battle against drug-resistant infections may just swing back in our favour. Natural products remain our best hope of treating disease but we know that resistance is inevitable. This means the battle will continue for as long as humans survive because we will always need new antibiotics.

MATT HUTCHINGS, University of East Anglia, LORENA T. FERNÁNDEZ-MARTÍNEZ, John Innes Centre & PAUL A. HOSKISSON, University of Strathclyde

A taste of honey

Ian Richardson & Annabel Large

THE EXTENDED ESSAY is an essential component of the International Baccalaureate diploma course for students studying at Rydal-Penrhos School in North Wales. Students have to decide on a subject and a specific area of interest early in the lower sixth. In biology, they are encouraged to research their chosen area and develop research and practical skills. Both organisation and planning are crucial, especially in a practical-based subject. They must learn to work within a department and plan the use of resources and lab time. This is done under the watchful eye of a supervisor, who guides and provides a framework in the form of checkpoints over the year to monitor progress.

This year we were fortunate for one student to establish a link with the SGM that enabled us to utilise their knowledge and resources – the link was established after a speculative phone call. The antimicrobial properties of honey was at the heart of the discussion after the student, Annabel Large, had read various articles about manuka honey and its historical use as a treatment against bacterial infection. It was not long after this initial contact that Annabel was advised to contact various University lecturers and the whole project suddenly burst into life. The whole experience has been very positive from a supervisor's point of view and I am very grateful for the time and effort the scientists have invested in Annabel's project.

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INITIALLY, I WAS QUITE DAUNTED by the 'extended essay'; I had no idea what topic to pursue, what was accessible or most appropriate. However, I was clear that it was going to be a science-based project. A BBC news article discussing honey also inspired me with its potential to act as an antimicrobial agent to counter hospital-acquired infections like MRSA. This had me captivated to think that a substance like honey could be used to breakdown and weaken a complex resistant strain of bacteria that has been troubling the medical profession for years. At this point I was advised to contact the SGM, I wasn't expecting much feedback as a sixth form student and did not think anyone would be that interested. But, I was absolutely taken aback by the response I received. The SGM team put me in contact with Jenny Hawkins at Cardiff University and Dr Sarah Maddocks, an associate lecturer at Cardiff School of Health Sciences. Both replied in great detail and right from the start they reassured me that it would be possible to conduct an experiment to replicate some of their findings. They sent further articles, research papers and even discussed general methodology and appropriate microbes to use. They introduced me to the '*Microbiology Twitter Journal Club*', which I logged onto and received insightful findings from other researchers.

Annabel in the lab. *I. Richardson*

As a result of this input my research question was conceived, '*Do the antimicrobial properties of regional honey differ to manuka honey and how could these unique antimicrobial properties be incorporated in modern medicine in the fight against resistant strains of bacteria?*' The use of local honey was unique in my project because both centres had never tested honey from North Wales. As a result of the collaboration I agreed to supply the honey I tested to both research establishments.

Throughout my investigation, I had continued support from these leading researchers and I would strongly advise anyone to do the same. Although challenging at times, it has been an extremely worthwhile and exciting experience. I owe a great debt of thanks to the SGM staff and Dr Maddocks and Jenny Hawkins in Cardiff. I am happy to report the first draft is now written and I am well on the way to completing the task!

ANNABEL LARGE

Journal publishing – what happens between submission and publication?

You've written your first paper, you've selected a journal to submit it to (using the advice offered in the August 2012 issue of *Microbiology Today*) and now you're ready to send it through the peer-review process. If you haven't done this before it can be daunting and there are mistakes that can be made that can either slow down the process or, worse still, result in the receipt of a rejection letter. Karen Rowlett, Managing Editor of the *International Journal of Systematic and Evolutionary Microbiology*, gives Karen McGregor some insight into what you should expect during the process from submission to publication.

Q *What is your number one tip for authors?*

A Read and stick to the instructions for authors of the journal you are submitting your paper to – it seems obvious, but it is not always done. If you submit a manuscript in a format that doesn't strictly conform to the instructions laid down by the journal it is likely that your paper will be returned to you, delaying the whole process. Equally important is to make sure that the contact details for the corresponding author are correct – particularly the email address. There are a number of steps during the process where you will need to be contacted so make sure you use an email address that will be monitored regularly and will be active throughout the process (if you are coming to the end of your PhD don't use your university email address if there is a chance that that account will be closed in a few months' time).

Q *What should go in the covering letter?*

A A covering letter is a useful way of introducing your research to the journal Editor. Remember, Editors may handle hundreds of papers a year and may not be fully up to date in every area – this is why they rely on specialist reviewers. If you explain the relevance of your research (and possibly include references to other recently published papers or papers in press), you will give the Editor a better idea of the significance of your findings.

If there is a good reason why you would like a quick decision on your paper, for example, to fulfil the requirements for a PhD defence, let the Editor know in your covering letter. They may not be able to expedite review, but if they are aware of the deadline they may be able to help.

Q *How can the author identify appropriate editors/reviewers to suggest?*

A Most journal submission systems will ask you to suggest an Editor and potential reviewers for your paper. The journal website will list the names of the Editorial Board for the journal and may give some guidance on the types of paper that each Editor handles. You may also have the option to exclude individual Editors from handling your paper; think carefully about this and only exclude Editors if there is a very good reason for doing so, e.g. they are in direct competition with your laboratory.

Reviewers should have an understanding of the scientific concepts in your paper. If you have completed a literature review or attended relevant conferences, you may be able to identify appropriate reviewers easily. Talk to your supervisor or other members of your department if you need additional suggestions. 'Jane' (**J**ournal/**A**uthor **N**ame **E**stimator, www.biosemantics.org/jane/) allows you to input the abstract or title of your paper to identify authors that publish similar work. Don't suggest inappropriate reviewers – Dr Jo Blogs who works in the lab next door may have a very good opinion of your work but would not be a suitable reviewer. In general, reviewers should not work at your institution.

If your paper has already been rejected by one journal, make sure that you reformat the manuscript according to the style of the next journal. If you don't do this, the paper will be returned to you and it may also be obvious to the Editors that the paper has been submitted elsewhere first (particularly if you forget to change your covering letter!). Editors don't like to think that their journal might be a second choice.

Q *How should the author respond to reviewers' comments?*

A Make sure that you prepare a response to all of the reviewers' comments. If you do not agree with a comment, give a clear reason why you think that the change is not necessary, don't just ignore it. When you upload your point-by-point response to reviewers with your revised manuscript, it can help the Editor if you create a separate version of your manuscript with the main changes highlighted or in a different coloured font; this makes it easy for them to check that all the required changes have been made.

Keep a note of the revision deadlines imposed by the journal Editor. If you know that conducting extra experiments within this time frame will be difficult, let the Editor know well in advance and they may extend the deadline for revision.

Q *If the paper is rejected what are the author's options?*

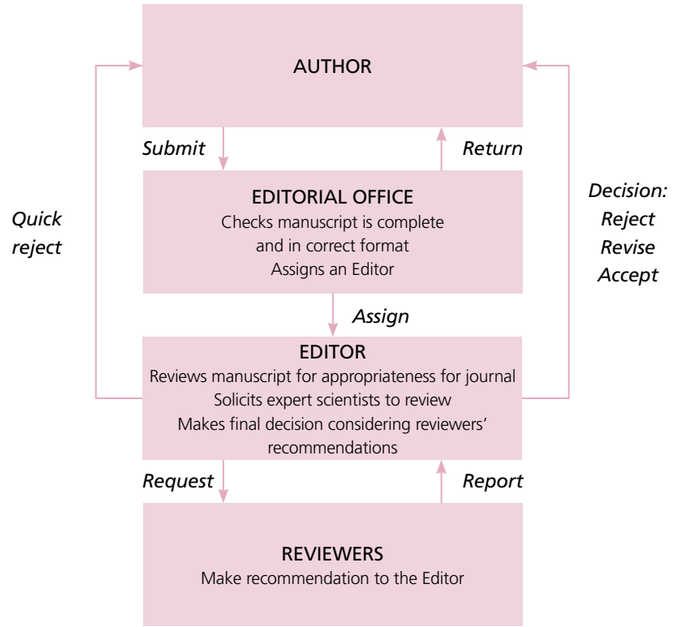
A Rejection is a reality of the process and some journals, particularly high-impact ones, have very high rejection rates. Rejection may not necessarily mean that your paper is not of good quality, it may just mean that it is not appropriate for that journal. Sometimes Editors will reject a paper but encourage resubmission once particular problems have been addressed.

Some large publishers operate 'cascade journals'. Your rejection letter may suggest submission to an alternative journal within the same publishing group. The second-tier journal will have a lower impact factor but may still be a suitable home for your paper. If you decide to pass the submission to the next journal in the 'cascade', you won't need to reformat your paper and the reviewers' comments may go with it to the next Editor. This could lead to a quicker decision than starting the submission process again with a new journal. However, you should think about whether the second-tier journal is actually the best place for your paper; could it be improved and submitted elsewhere?

Q *What happens after the paper is accepted?*

A Receiving an acceptance letter is by no means the end of the process. In the acceptance letter, the Editor may suggest some further minor changes; if so, make sure that you do these quickly.

After acceptance, your paper will be prepared for publication by the journal's editorial team. Depending on the type of journal, this may involve some copy-



Flowchart illustrating the journal review process.

editing and reformatting of your manuscript. The editorial team may need to contact you at this stage if they have any queries relating to your manuscript such as missing references, and inconsistencies between results in the text and tables or figures. You may also be asked to submit the source files for any images if the versions that were submitted for review are not suitable for final print or online publication.

Once your paper has been converted to journal format, you will be sent a proof of the typeset paper. Check the deadline for returning the proof – it could be only a few days as journals often have very rigid production schedules. Look at the proof very carefully – this will be your last chance to check that the text is correct and to put right any minor mistakes (but it is not the time to make extensive changes!). As you will be very familiar with your paper by now it can be very easy to overlook mistakes, so why not get a colleague to check it too? Mark the proof up very clearly (there is no need to use 'proper' proof correction symbols as long as your instructions are clear). If you need to insert several lines of text or a reference, type this out in an email so that there is no possibility of misread handwriting.

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Once that is done, you can sit back and look forward to seeing your name in print – or get started on your next paper and go through the publication process all over again!

Opportunities for UG students

SGM SUPPORTS undergraduate (UG) students who would like to experience a scientific conference. UG student members who register for the SGM Spring 2013 Conference in Manchester before the earlybird deadline on **Friday 22 February** will not pay a registration fee to attend the conference. Those who have results to present can apply for a UG Student Conference Grant to contribute towards their travel and accommodation costs. Students need not be the first author, but should be present at the poster session to talk about their work. The research being presented may have been done at any point during their UG studies, including a placement year, final-year honours project or vacation project.

Three UG student members – **Helina Marshall**, **Kathryn Turnbull** & **Lisa Buddrus** – received funding from SGM to present work at the SGM Autumn 2012 Conference in Warwick (3–5 September). Helina who had just completed a BSc (Hons) in Biological Sciences at Edinburgh Napier University talked to Karen McGregor about her experiences.

'I've been a UG member of SGM throughout my degree and I always wanted to attend a conference. For part of my final year honours project I carried out a 3-month full-time research project at the Moredun Research Institute. When the results of the project turned out to be novel and not wholly what we expected, we thought it was worth talking about.

Helina Marshall (left) and Kathryn Turnbull (above right) presenting their posters at the SGM Autumn 2012 Conference at the University of Warwick. *I. Atherton*

Attending the conference was better than I could have expected – I met some really great people and attended talks about the exciting new work going on in different fields of microbiology (and, having just finished my degree, was pleasantly surprised at how much I understood – I was a bit worried before the conference that I might end up feeling a bit stupid). Presenting the poster was a little daunting at first, but it was a really great experience. Discussing my work with other people, seeing people interested in my results and getting their suggestions of what could be done next with my research was really inspiring. I just generally enjoyed the whole conference experience! It has definitely made me more certain about continuing into a career in research and I have just started on a BBSRC interdisciplinary doctoral training programme based at University College London.'

Lisa Budruss gave an oral presentation entitled *Electricity generation in MFCs using distillers' dried grains with solubles* and recorded a podcast with the SGM Press Officer about her work. Listen at **http://bit.ly/RWGvCO**

Grants – make the most of your membership

Information on all SGM grant schemes available in 2013, together with application forms can be found at **www.sgm.ac.uk/grants**

HARRY SMITH VACATION STUDENTSHIPS

These studentships enable UG students to work on microbiology research projects during the summer vacation before their final year of study. They provide support to the student at a rate of £185 per week for a period of up to 8 weeks plus up to £400 for laboratory consumables.

Applications should be made by SGM members who will act as the project supervisor on behalf of a named UG student.

Closing date for applications is **15 February 2013**.

CAREERS CONFERENCE GRANTS

These grants offer UG Student Members a contribution towards registration fees and cost of travel to a Life Sciences Careers Conference. Aimed at UGs and recent graduates, the conferences include presentations covering a wide range of science-related subjects, a CV workshop providing tips on how to secure an interview for your perfect job, and a chance to mingle with the experts exhibiting at the conference and ask informal questions over lunch and afternoon refreshments.

The 2012 conferences are taking place at University of Birmingham on Wednesday 14 November 2012, Queen's University Belfast on Wednesday 28 November 2012 and University of Leeds on Wednesday 5 December 2012.

INTERVIEW

Ian Boyd Defra Chief Scientific Adviser

SGM would like to congratulate you on your new appointment as Chief Scientific Adviser to Defra, and wish you well in the role. We appreciate that you've not had much time to get to grips with the full gamut of responsibilities you will have from September, but nevertheless we have a few questions on your work as it relates to the interests of our members.

YOUR ASPIRATIONS AS CHIEF SCIENTIFIC ADVISOR

Q *How do you think your career so far has helped prepare you for the role of Defra Chief Scientific Adviser? Are there lessons for our members who wish to take a role in setting and implementing policy at a senior level? What are your ambitions in the role?*

A My career has seen me spend considerable time in both research institutions and universities so I am aware of the structural, cultural and functional differences among these research delivery bodies. Added to this, as an academic researcher I made a specific point of spending time working on policy-related issues. I made an intentional choice to sacrifice time that I could have spent following my own research interests in order to oil the wheels at the science–policy interface. This was deeply unfashionable within universities even just a few years ago but the changes in the structure of the Research Excellence Framework towards recognition of impact have changed this. I was very fortunate to have understanding management at St Andrews. The main message is that intellectually agile individuals, wherever they are and whatever they are studying, should have the capacity to connect their research with societal benefits and should be continually exploring and probing how best to achieve this. If I can help to significantly raise the game of the science research community with respect to how they work within policy and with industry then I will have made a difference. We are faced with some massive challenges over the coming decades and I want the best and most imaginative minds to be brought to bear on coming up with solutions.

Q *The government has emphasised agriculture as a route to 'export-led growth'. From some angles, Defra can sound like the old Ministry of Agriculture! But the department now has many additional responsibilities. How do you see the relative emphases in your new role – and where do your priorities lie?*

A Some of the old images of 'The Ministry' are certainly hard to shake off. This is partly because Defra retains the old role of regulator in agriculture and fisheries, and this is now extending to other uses of the environment. There is a very real image problem associated with this because it is all too easy for Defra to be seen as a bureaucracy that interferes in people's lives. I see my role as partly being there to explain the rationale, based upon the evidence, for why Defra needs to take certain views and build policies that sometimes might appear counter-intuitive. This is not just about ensuring that policies are firmly grounded in core science, but it is also about integrating this with social and economic evidence and being able to take a long-term view. It is hard to persuade people of the benefits of a policy that is designed to smooth our path over decadal time scales when it is not seen to have tangible benefits here and now. Communicating these concepts is extraordinarily difficult and a priority for me is to both listen to people's concerns and to explain the evidence upon which policies are based.

Q *Defra already draws on a wide portfolio of scientific expertise – in its own research establishments, in agriculture and industry, in institutes funded by the Research Councils, in learned societies, and in universities. How will your role fit into this network?*

A The UK has a rich and diverse mixture of mechanisms for undertaking scientific research. I think this is one reason why the UK, considering its size, has been and remains a leading global economic power. I sometimes get frustrated by narrowly focussed metrics produced by individual institutions to make them look better than others. We all know that different institutions play different roles in the mixture. While there are weaknesses which need to be addressed, this isn't a case of one type of research delivery mechanism being better than another. The real question concerns how, in functional terms, each one delivers high-quality science to support societal objectives and on what time scales. Each institution presents a different profile in that respect and consequently is optimised differently. I can fit into this by helping Defra to exploit this diversity by drawing down the best quality of evidence from across the whole spectrum of providers and also to provide constructive feedback about how the flow of evidence could be improved.

Ian Boyd. *Defra*

THE MARINE ENVIRONMENT AND MICROBIOLOGY

Q *You have had a distinguished career in marine biology, and microbiologists have a particular interest in disease in aquaculture, natural products from marine micro-organisms and microbial pollution (algae and bacteria). Does Defra have any particular plans in these areas you can tell us about?*

A I have spent my career studying 'big things', basically from very large multicellular organisms up to large-scale ecosystems. However, one of my interests is in scale-free processes so the size of 'things' becomes less relevant. As I said in a recent perspectives piece in *Science*, the dynamics of yeast cultures can help to explain the dynamics of much larger-scale systems. I find the whole idea that the same basic mechanisms govern dynamic systems from the very small to the very large utterly gripping; if we can find the fundamental key to understanding these common processes then we will have made a major intellectual leap forward. Bringing this back to the very real problems of biosecurity, the exploitation of microbial processes and managing microbial ecology is a very important challenge.

CROP AND LIVESTOCK DISEASES

Crop and livestock diseases – a big issue, and a complex one, but also one very dear to the professional lives of many of our members. Three questions:

Q *What are your aspirations for Defra's research on infectious diseases of crops and livestock?*

A The UK agricultural system, including forestry, is probably under greater stress from new infectious diseases now than at any time in history. This presents a critical national challenge and it is not just Defra that has to step up to meet this but the research community as a whole. However, it is Defra's job to take a lead in tackling non-indigenous crop diseases both in terms of providing targeted resources and developing strategies that others can align with. This needs to include the whole spectrum of control measures from protection and mitigation through to adaptation, when we are aware that protection and mitigation are unlikely to work. But, at the centre of this will also be communication both within the research community to help align the best minds to tackle the most pressing problems in a way that will likely make a difference, and with the public whose lives, livelihoods and environment might be seriously altered as a result.

Q *What balance between endemic and (potential) 'exotic' disease threats do you think works best in the research and surveillance portfolio?*

A Livestock diseases can have significant economic, social and environmental costs in addition to compromising the welfare of affected animals. Also, an outbreak of an exotic notifiable disease can have severe trade implications for the UK economy. Defra's current research and surveillance

portfolio funds work on a number of different diseases, both endemic and exotic, and it is important to remember that they are not mutually exclusive. For example, adherence to strong biosecurity principles for endemic diseases may reduce the potential impact of an exotic disease. Defra's surveillance programme is targeted towards the detection of new and re-emerging threats, aligned with a reactive research programme enabling us to respond effectively. On the question of whether we always have the balance that works best – that is a question that is difficult to answer, but I recognise that it is vital to constantly monitor and evaluate our research and surveillance programme to ensure that it continues to address the threat. What is important is that we maintain the UK's expertise and capability to act quickly no matter whether that threat is from an exotic, endemic or indeed a new and re-emerging disease.

Q *The issue of microbial food safety is always with us and occasionally erupts as a crisis. How will you scan for impending crises, gauge their scale, and communicate the risk to ministers? How can professional microbiologists and learned societies like SGM assist you in horizon-scanning?*

A The issue of food safety sits with the Food Standards Agency, but it is right that Defra should take an active interest in the issue, especially where environmental factors are a major cause. Defra invests heavily in the assessment of risk and it is possible to develop reasonably accurate predictions of the occurrence of problems with microbial food safety. The major problem is assessing the extent to which these predictions might be challenged by the effects of climate change or changing human behaviour. The early detection of trends is essential and, like any infectious disease that affects people, there needs to be a strong link between health screening through the NHS and the response to an outbreak.

Q *What position do you take on the use of antibiotics in agriculture?*

A Antibiotic resistance is a major problem and we need to properly assess the costs and benefits of antibiotic use. It would be easy to just say we should stop all antibiotic use, but there are likely to be key types of uses that present greater problems than others. I also have to point to innovation as a route through this problem. Not only do we need a continuous stream of new antibiotics, perhaps even more importantly, we need to adapt our systems of agriculture to be much more aware of biosecurity. I suspect there is a lot that can be done to achieve this, mainly representing relatively simple control measures, but the challenge is in communicating this and incentivising individual practitioners to implement these measures.

AND FINALLY…

Q *Your website refers to your scientific interest in the 'Behavioural dynamics of marine predators'. There are almost certainly a few killer whales lurking in Whitehall. How can scientists avoid getting eaten alive – or do scientists have nothing to fear from these 'majestic predators'?*

A My experience of working with politicians and policy people is that they are really not very different from scientists. The competitive nature of scientific research certainly doesn't leave much room for the faint-hearted or thin-skinned these days. In general, we are all rational people who make decisions based upon a combination of the evidence available and prejudice or belief. What distinguishes scientists from the others is that they perhaps lean more towards decision-making based upon evidence, at least professionally. Scientists have a very important general mentoring role in trying to make others think outside their box, often by presenting evidence in ways that cause others to question their prejudices or beliefs. I may be proved wrong, but I think the metaphor of the killer whales prowling Whitehall is not really accurate. Certainly, there are some difficult trade-offs to be made at the top level of government and one can find oneself on the losing end of an argument, but we live in such an imperfect world that one cannot afford to take the rough time personally. I would encourage more scientists to get involved and not to be afraid to do so. Even if you do feel you have been 'eaten alive' in the process, it can be very rewarding to see your ideas taken up by the government machine and used, hopefully, towards a positive outcome for society.

Marjory Stephenson and me

Hilary Lappin-Scott

Marjory Stephenson. *SGM*

Hilary Lappin-Scott. *I. Atherton, SGM*

There is a need for greater diversity in our scientific 'mixed community' to strengthen microbial sciences and the SGM.

AT FIRST GLANCE Marjory Stephenson and I do not have much in common. She went directly into academia from school, was one of the first two females (with Kathleen Lonsdale) to be elected to the Royal Society and served as President of the SGM immediately after Alexander Fleming in 1947–1949. As the years rolled by, the SGM rose in eminence, successive Presidents were appointed, but we had to wait until 2009 before a second female held this office (me), a period of some 60 years after it was held by Marjory Stephenson. I worked for several years before going to University, I am the first scientist/academic in my family and briefly held the SGM Presidency concurrently with that of the International Society of Microbial Ecology.

Thankfully, there are now more women in the workforce than in Marjory Stephenson's time, but generally they occupy the lower levels, with few reaching the top jobs in industry, government or academia. Microbiology attracts many females at undergraduate and postgraduate levels, but the numbers then dwindle with every successive step up the academic ladder, often referred to as the 'leaky pipeline of talent' (www.royalsoced.org.uk/cms/files/advice-papers/inquiry/women_in_stem/tapping_talents.pdf).

Throughout my career I have of course been aware that at each career stage there have been fewer and fewer females around the table with me. I have always considered that the best way to address this was to lead by example, by striving to be a strong role model in all my activities and to mentor female and male early- and mid-career scientists. I enjoy these roles and consider that they are part of the job.

This changed when I became more involved in social media and, significantly, because of the recent EU campaign *Science: It's a girl thing*. Social media gives me daily access to a wide range of opinions outside of my usual activities and increases my awareness to the real concerns of early-career microbiologists (males and females) who are considering their future and how to balance careers with family life. The EU podcast has already been covered by others, I consider that it captures much of the complexity of how to attract all sections of society into science.

The presence of more males in senior roles is often attributed to committees considering only those '*in our own images*' when choosing who to invite to give talks, to be awarded scientific distinctions, to sit on prestigious committees, and who to encourage to apply for top jobs, etc. Suffice to state that this draws on a limited section of the talent pool, to the detriment of our discipline, and is a cause of growing concern within SGM.

When I completed my 3-year term of office as President in September, Council asked me to establish a new initiative as SGM Diversity Champion, to work to promote greater gender and ethnicity diversity by tapping more widely into our talent pool. A Working Group will shortly be set up to support this; however, I am keen to hear all ideas from the membership, to aid our success. Similarly, the Working Group will seek to learn from and work with other learned societies to address issues of equality and diversity.

After all, we understand all too well that monocultures do not reflect nature and that diverse communities give the greatest stability. We are determined not to wait another 60 years before there is another female President.

HILARY LAPPIN-SCOTT
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SGM JOURNALS

ALL SGM JOURNALS ARE NOT-FOR-PROFIT AND…

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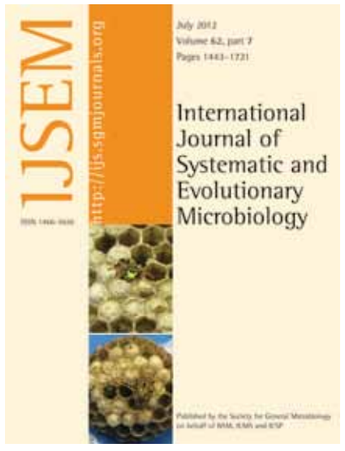
Microbiology, published monthly, combines editorial expertise from around the world with exceptional breadth of coverage and high-quality production standards, and provides access to topical, high-quality research and up-to-date reviews in a single accessible source.



IJSEM is the official journal of record for novel prokaryotic names of the International Committee on Systematics of Prokaryotes (ICSP) of the International Union of Microbiological Societies (IUMS). The journal is the cornerstone of the dynamic field of microbial systematics.

JMM, published monthly, is one of the leading peer-reviewed journals in the field, publishing high-calibre research papers, reviews, editorials, case reports and correspondence articles on medical, dental and veterinary microbiology and infectious diseases from around the world.

JGV is a dynamic journal at the forefront of virology today. Established for 45 years, **JGV** publishes high-quality virological research from around the world on a monthly basis.

Designer microbes make an appearance at SGM

Rocky Cranenburgh

Synthetic biology is a rapidly growing area of applied biotechnology that represents the fusion of genetic engineering with an increased understanding of the complex workings of cells that has come from genomics, transcriptomics, metabolomics and systems modelling. To highlight the latest developments in synthetic biology, there will be a special themed issue of SGM's journal *Microbiology* in July 2013 and papers are invited for submission from now to mid-January 2013.

THERE IS NO universally accepted definition of synthetic biology, but while it certainly encompasses applications of genetic engineering and biotechnology, it is fundamentally about the design and the introduction of new components or biosynthetic pathways into cells, or the adaptation of existing pathways to produce novel compounds or features. While traditional genetic engineering often involves mutating a chromosomal gene or inserting a new gene, synthetic biology describes the manipulation of biological systems, enabling cells to be designed that are capable of carrying out novel functions and/or producing new compounds. Recent developments in the enabling technologies, such as DNA sequencing and synthesis, have revolutionised what is potentially achievable by synthetic biology.

At the SGM Autumn 2012 conference in Warwick, I co-chaired a symposium on *Designer microbes*, which featured innovative advances in synthetic biology. Justin Buck (Cambrian Innovation Inc.) and Lisa Buddrus (Surrey) described the use of bacteria to generate electricity in microbial fuel cells. Although these approaches do not necessarily involve genetic modification, they do necessitate a detailed understanding of biochemical pathways to identify the best bacterial candidates as 'exoelectrogens', and the development of engineering solutions to maximise their potential. Biofuel production is an area where microbes could have an important role. David Leak (Bath) described his work on ethanol production using thermophiles, Thomas Howard (Exeter) focussed on transport fuel production in *Escherichia coli* and Aindrila Mukhopadhyay (Berkeley) described the use of microbial efflux pumps for biofuel tolerance and production.

Micro-algae are being developed to produce biofuels and other products, and Saul Purton (UCL) described the use of DNA components called 'Phycobricks' in synthetic biology applications of *Chlamydomonas reinhardtii*. Cellulosic biomass is an abundant and under-utilised resource, and Chris French's group (Edinburgh) engineer cellulose-degrading *E. coli* and *Citrobacter freundii* using enzymes identified from a range of other bacteria. Genetic engineering tools are critical to synthetic biology and Nigel Minton (Nottingham) described his ClosTron system for modification of *Clostridium* spp. Public perception and bioethics considerations will influence the development of synthetic biology, and Joyce Tait (Edinburgh) discussed the way that social scientists view technological advances, focussing on approaches to achieve smarter and more flexible regulation.

Synthetic biology is not restricted to industrial applications, and biomedical applications are still of the greatest commercial importance. Michael Bromley (Manchester) described the use of synthetic biology approaches in a screen to identify novel antifungal drugs. Our work at Prokarium (presented at the SGM Spring 2012 conference in Dublin) utilises live *Salmonella* that contain modified genetic circuitry to achieve selectable marker-free plasmid maintenance and targeted antigen gene expression for oral vaccine delivery.

The presentations at the *Designer microbes* symposium gave an overview of the applications of synthetic biology, indicating some of the areas that we are interested in for the *Microbiology* special issue, but we welcome articles on a wide range of synthetic biology topics and look forward to an interesting issue that will help to define this new and exciting field.

Papers for the special issue must be submitted by ***mid-January 2013****. Full details about the scope and how to submit are available at* ***http://bit.ly/PCbKVh***

ROCKY CRANENBURGH
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Email rocky.cranenburgh@prokarium.com

SB's new HE teaching website promotes Open Education Resources

Eva Sharpe

This summer, the Society of Biology (SB) received funding from the Higher Education Academy and JISC through their Open Education Resources (OER) Programme. We were to work with our Special Interest Group, the Heads of University Biosciences (HUBS), to identify, collect and promote UK OER to the bioscience community. Through this project, we have recently launched a new Higher Education (HE) teaching website at **http://heteaching.societyofbiology.org**

OER ARE LEARNING, teaching and research resources freely available for the teaching community to use and adapt that have been released under specific intellectual property rules. There are many excellent teaching resources publicly available across various websites, publications and discussion forums. Although some of these resources are featured in specific sites, such as the UK's national repository for OER, Jorum, many are hosted directly on institutions' own websites and may require extensive searching to find them.

The project allowed us to identify resources for bioscience HE, and signpost them to the teaching community via a new website, reducing the time spent by individuals searching the web, ensuring better access to quality teaching resources, and introducing and encouraging those who are new to OER.

Working closely with the HUBS Executive Committee to ensure the project meets the needs of those working in HE, we have focused on resources that support practical biology and research-led teaching in HE.

Over the summer we surveyed the biosciences community to find out what they would find most useful from the website. We asked about current use and barriers to using OER and comments on our plans for our website.

In response to our suggestion that we focus on practical biology resources, respondents felt that lab and fieldwork protocols, data handling exercises, videos of techniques and multimedia alternatives to wet lab work would be the most useful resources to feature.

Feedback from those already using OER highlighted that although there was a number of very good resources available, there was a huge variety in the quality, and a great deal of searching and sorting was needed to find high-quality resources. To address this we have included an element of peer review in the project, recruiting a team of experts in the bioscience teaching community to review all of the resources we find.

When asked about the main barriers to creating OER, the overwhelming response was, unsurprisingly, that of time, but many responded that they did not know how to go about releasing their teaching materials as OER, or even whether their institutions would allow this. Resources such as the JISC OER infokit and STEM OER Guidance wiki provide information on using and creating OER, covering copyright and intellectual property issues, and 'dos and don'ts' for creating your own resources.

The uncertainty over whether institutions allow and encourage their staff to create and release OER is something we all need to address as a community. Institutional policy needs to be disseminated and embedded at a departmental level and departments need to make it clear what staff training is available to support this. In our work with departmental heads through HUBS, and teaching practitioners in our membership and beyond, we will be promoting institutional change to support the use of OER and championing reward and recognition for those involved.

Setting up this new website to promote the use of OER has been the start of this project for us, and we look forward to working with you all on this in the future. We will be adding new resources as they are released to keep the website up to date and useful. If you are creating new resources, or know of a great resource that we have missed, then please let us know via the 'Submit resources' section of the site!

For more information on the project please see **http:/heteaching.societyofbiology.org**

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USEFUL WEBSITES
www.heacademy.ac.uk
www.jisc.ac.uk
www.societyofbiology.org/hubs
www.jorum.ac.uk

Influenza Virus: Methods and Protocols

Edited by Y. Kawaoka & G. Neumann

Published by Springer-Verlag GmbH & Co. KG (2012)

£85.50 pp. 234 ISBN 978-1-61779-620-3

This book really does do 'what it says on the tin'. One of the *Methods in Molecular Biology* series, it covers much more than just molecular biology. Chapters cover a comprehensive list of topics, such as virus isolation, characterisation of the virus, serological methods, diagnosis of influenza, laboratory assays, animal models, surveillance, molecular virology techniques, genetic analysis and genetic engineering of the virus. The chapters are all extremely informative both for a new researcher in the field or for the more seasoned flu researcher, and I think this book would be a valuable addition to the laboratory bookshelf. Influenza virus will continue to challenge and no doubt surprise us. This really is a multi-disciplinary book, which I personally think is very beneficial, as influenza researchers need to be able to approach research from all angles to try to stay one step ahead of an ever evolving virus.

RUTH HARVEY, National Institute for Biological Standards & Control

Microbes and Evolution: The World That Darwin Never Saw

Edited by R. Kolter & S. Maloy

Published by American Society for Microbiology (2012)

US$14.95 pp. 299 ISBN 978-1-55581-540-0

Initially stimulated by the bicentenary of Darwin's birth, this collection of essays discusses how microbes fit evolution as Darwin would have understood it. There are good examples of classical Darwinian evolution and cases where we have to bend our ideas somewhat.

Metaphor is a powerful tool for conveying concepts to a lay audience. Unfortunately, it ends up being confusing when the metaphor shifts every few pages. This is not, then, a book to be read from cover to cover, at least not in one sitting. It is also unclear at whom this book is aimed. Many chapters would be clear to any intelligent reader, but others seem to be written for an audience of microbiologists or molecular biologists. That said, there are some excellent essays in this collection and I shall use ideas from it when teaching the concept of microbiology to general biologists.

DAVID ROBERTS, The Natural History Museum

Systems Microbiology: Current Topics and Applications

Edited by B.D. Robertson & B.W. Wren

Published by Caister Academic Press (2012)

£159.00 pp. 170 ISBN 978-1-90823-002-7

This compact volume contains contributions from many well-known names in the field of systems microbiology. The book opens with an overview of modelling approaches which, as an experimental microbiologist, I found particularly interesting and valuable. This is followed by chapters on microbial phenomena, such as chemotaxis and phagocytosis, and on the metabolic pathways of single species of bacteria and archaea. The theoretical and modelling approaches presented within these case studies are clearly explained and, similarly, the biological information is written in such as way as to make it accessible to non-specialists. Each chapter contains numerous references for those interested in investigating a particular topic in more detail. The wide range of biological and modelling topics covered would make this a beneficial purchase for any institution or systems biology consortium. Overall, this is a valuable resource that will appeal to experimentalists and modellers alike.

ALISON GRAHAM, Newcastle University

Genome Plasticity and Infectious Diseases

Edited by J. Hacker, U. Dobrindt & R. Kurth

Published by American Society for Microbiology (2012)

US$159.95 pp. 416 ISBN 978-1-55581-708-4

Variety is, supposedly, 'the spice of life'. In the case of infectious agents, however, it is a matter of survival. Genomic plasticity in infectious agents is alteration of the sequence of genes so that different sequences are expressed or the original sequences are expressed at different levels. This phenomenon allows those infectious agents to adapt and survive changes in their environmental conditions. In the context of infectious disease, the environment includes the host, so genomic plasticity in the host organism also has to be considered. This book describes examples of genomic changes occurring in medically important bacteria, viruses, fungi and protozoa, as well as examples of genomic plasticity that occur in man that affect susceptibility to these agents. Changes can occur by rearrangement within an organism's own genome or by the addition or exchange of genetic material from outside, and any genomic change that enables an infectious agent to survive, flourish and, in some cases, cause disease, in an environment made evermore hostile by the presence of antimicrobial drugs or host immune responses, will be to the agent's advantage.

The book would benefit from the inclusion an introductory chapter describing the basis of genomic change and its relevance to infectious disease, and also by having abstracts in each chapter. The book will be of interest to anyone studying infectious diseases but its price will certainly limit purchase to institutions.

CHRISTOPHER RING, Middlesex University

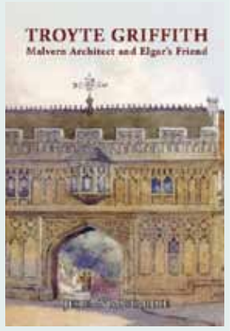
Troyte Griffith, Malvern Architect and Elgar's Friend

By Jeremy Hardie

Published by Aspect Design (2012)

£12.50 pp. 164 ISBN 978-1-90883-210-8

Having reached the dizzy heights of Professor in Microbiology, retirement looms. But what happens then? Is there anything from all those years of knowledge acquisition and experience that can be combined with the gardening and holidays? Do all those hard-earned skills have to be lost the day one walks out of the department? A recent publication exemplifies how well the training in research investigation, writing and presentation can be reborn in a very satisfying way.



Deep in Elgar's homelands amongst the beautiful Malvern Hills, curiosity drove Emeritus Professor of Oral Microbiology (St Barts and the London School of Medicine and Dentistry, University of London), Jeremy Hardie, to find out more about the history behind the house he bought to enjoy his retirement in with his wife Margaret. Why did the architect who designed the house become immortalised by Elgar because one of his Enigma variations bore his name? Unlike most of the other subjects of Elgar's portrait gallery, Troyte Griffith was not a gifted musician.

The book brings together the architectural impact that Troyte Griffith had and delves into his relationship with the famous composer in a readily readable way with lots of interesting illustrations.

With acclaim in the local press (*Malvern Gazette* and *Birmingham Post*), the book is available at several bookshops and libraries specialising in local history, architecture or music-related material.

KIM HARDIE, The University of Nottingham

COMMENT

ANTIBIOTIC ACTION

TRACEY GUISE & LAURA J.V. PIDDOCK

'If health fails, all else fails' said Margaret Chan, Director General of the World Health Organization (WHO), in her 62nd address to the Regional Committee for Europe in September 2012.

She had just spoken of the need to tackle the major health and social issues required to meet the WHO Millennium Development Goals leading to improved health for all by 2015. High on the list of stated priorities was the need to tackle the continued rise in antibiotic-resistant bacteria and the lack of development of new antibiotics.

Her words resonate loudly with *Antibiotic Action*, the UK-led global initiative that exists to inform and educate all about the need for discovery, research and development of new antibacterial drugs. Launched at the Houses of Parliament in November 2011, the initiative received unprecedented interest and support. Organisations across the globe sought to partner and support *Antibiotic Action*, manuscripts were accepted and published by esteemed international peer-reviewed journals, stories were written in newspapers and magazines and broadcast on radio and television. *Antibiotic Action* gained a respectable following on Twitter, an Early Day Motion was presented to the House of Commons and thousands of individuals signed the online petition. It was an explosive start to an initiative that began by examining why, after over a decade of esteemed publications, committees, reports and professional concern, they had failed to generate sufficient interest to prevent the rapid decline in antibacterial drug discovery research and development.

So almost 12 months on, what has *Antibiotic Action* achieved? Highlights include:

- Collaborations with international groups, including ReACT, the Infectious Diseases Society of America, Alliance for the Prudent Use of Antibiotics and L'Alliance (representing 27 EU nations).
- Meeting the Health Minister Simon Burns and civil servants in the Department of Health. We now provide briefing documents.
- Meeting the Shadow Health Minister Jamie Reed, and provision of questions for the Prime Minister to answer in the House of Commons.
- Provision of administrative support to establish the All Party Parliamentary Group on Antibiotic Discovery and Development.
- Providing the momentum to stimulate revision of the regulatory processes for licensing new antibiotics.
- Discussions with the WHO to

help them deliver their action plan on antibiotic resistance – particularly in the area of public engagement.

- Facilitating public awareness and engagement by establishing an international network of *Antibiotic Action* Champions – some of whom have already successfully 'flown the *Antibiotic Action* flag' at student festivals and international conferences.
- Discussions with major funding bodies, such as the BBSRC, MRC and Wellcome Trust, on what can be learnt from industry to understand why some drug discovery programmes have not yielded new drugs.

The need for new antibiotics and the devastation the absence of antibiotics will wreak is undeniable. However, it will take time to alter perceptions about the urgent need to develop new antibiotics – that or a cataclysmic event to grow public understanding – just think of the furore if Prince Philip's recent bladder infection had been caused by an antibiotic-resistant bacterium which proved untreatable. We need to change the perception that antibiotics have failed – they have not – they are one of the miracles of modern medicine and the reason why many of us have reached adulthood today and will reach the extremes of age. As there is no collective memory of the pre-antibiotic era, the public voice is small, unlike that for other diseases such as cancer that many people are afraid they will die from. *Antibiotic Action* seeks to raise the voice to a deafening level so that everyone is aware that antibiotics underpin much of modern medicine from trauma to transplant surgery to joint replacements, and that infections are commonplace in these settings; governments and policy-makers must sit up, take note and act.

It has been proposed by many that it is financial incentives that will tempt industry to re-enter/continue to discover, research and develop new antibacterials as drugs for patients, and the recent GAIN Act in the USA and the EU Innovative Medicines Initiative seek to do this. It has been suggested by some that neither of these will have much impact; however, it is impossible to determine what the outcome will be and it is almost certain that it will take many different strategies and funding streams to resolve the situation. In particular, as microbiologists we must fight for our discipline to be heard equally with others that have high profiles. To do this we must make sure that the fantastic advances being made in academia are publicised and that there are mechanisms to facilitate development into new drugs. Links between academia, SMEs and Pharma require strengthening and new funding routes. In this way we can ensure that we retain the existing expertise and attract the brightest young minds to our fields of research, to discover and develop antibacterial drugs of the future. *Antibiotic Action* will continue to stimulate activities across disciplines to ensure new effective treatments are available. After all, without antibiotics the health of nations will fail – a fitting adjunct to the quote by Margaret Chan.

TRACEY GUISE, CEO British Society for Antimicrobial Chemotherapy (BSAC) & LAURA J.V. PIDDOCK, Professor of Microbiology, University of Birmingham, BSAC Chair in Public Engagement and Director of Antibiotic Action (*Email* l.j.v.piddock@bham.ac.uk)

We continue to seek new Antibiotic Action Champions, the remit of whom is simple, to inform as many people as possible of the need to discover research and develop new antibacterial drugs. If you wish to be a Champion please see the website for the resources we provide ***http://bit.ly/SHK5TC*** *or contact Laura Piddock.*

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