Microbiology TODAY

46:4 November 2019

Natural Products and Drug Discovery

Actinomycetes as nature's pharmacists
Breaking barriers with garlic
Manuka honey: potential from beehive to bedside
Burkholderia bacteria: natural alternatives to synthetic pesticides
Antimicrobial resistance, antimicrobial peptides and drug repurposing

MICROBIOLOGY SOCIETY

Editorial

Welcome to the November edition of *Microbiology Today*, the last one for 2019! This time we are addressing the wonderful world of drug discovery and natural products. The natural world has provided us with a huge diversity of products, which have been utilised for everything from medicine to pesticides. The sources of the natural products can themselves be from a variety of places and include products produced by micro-organisms, plants and animals.

Whole Picture

The discovery of a novel molecule is often the very first step in a long process, leading to a functional product that we then see in wider circulation. Our authors provide an insight into some of the current research that is advancing natural products for microbiology.

First to take us into the world of natural products is Lorena Fernández-Martínez, who brings us the actinomycetes. Highlighting the role these micro-organisms have had over the years, she gives us a real appreciation of the impact these bacteria have had in antimicrobial compound development. Describing the diversity of products that have come from these micro-organisms, Lorena discusses how new culture approaches might lead to the discovery of previously hidden compounds.

It is not just micro-organisms which can produce compounds with antimicrobial activity, and taking us from micro-organisms to plants, Heather Graz gives us some insight into the research and development steps necessary to turn something like the humble bulb of garlic into a registered pharmaceutical product. Addressing both the science and the business involved in natural product design, Heather suggests how research in this field could move forward.

On to a substance that needs input from both plants and animals, Aled Roberts discusses the role for honey in infectious disease control, highlighting how variation between different honeys affects their antimicrobial activity. Drawing on research which elucidates how manuka honey can inhibit bacteria in different ways, Aled addresses how this natural product could be used to help in the fight against antibiotic resistance.

Next, we shift our focus from medical to environmental, with Alex J. Mullins and Eshwar Mahenthiralingam explaining how *Burkholderia* have shown potential as natural alternatives to synthetic pesticides. With a growing world population that needs feeding, the need for safe and effective pesticides to protect food crops is becoming ever more important. Alex and Eshwar discuss the genomics which have led to the identification of key genes in these bacteria, and also the challenges involved when designing a product that will be released into the environment.

While prospecting around the globe in the hunt for natural products, we sometimes forget to take a closer look at what we already have. Thomas Vorup-Jensen, Stig Hill Christiansen and J. Eskild Petersen look at how drug repurposing can create useful antimicrobial agents. Addressing delivery, toxicity and development costs, they demonstrate how rational experimental design can uncover effective antimicrobial candidates from compounds originally designed to treat non-infectious diseases.

Finally, with the business end of drug discovery in mind, Michael Bagnall gives us the inside track on the various issues which can impact drug discovery and natural product development from a manufacturing point of view. Reminding us that discovering a promising natural product is only the very start of the process, Michael outlines the complex and ever-evolving factors which need to be considered before a product can reach its intended market.

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MICROBIOLOGY SOCIETY

Council 2019

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From the President

My tenure as President is taking place as the Society turns 75, and it promises to be a year to remember. The Society's Annual Conference will be in the beautiful city of Edinburgh in 2020. Annual Conference 2020 will be preceded by the Fleming Showcase, a celebration of microbiological science with eminent scientists speaking and discussing key topics in the field.

The event will also focus on the future of microbiology and early career researchers will be presenting their work. Abstract submission for Annual Conference 2020 is open online until Monday 9 December, so do remember to submit your abstract to ensure you are part of the event. You can also book to attend the Annual Conference 2020 and the Fleming Showcase on the website.

There have been a number of submissions for the 75th anniversary Microbiology Images project, including my own, showing the position of proteins. Images can be easier to share and help explain the context of research; they can inspire and engage people who may not know how intricate and visually stunning microbes can be, or how science is done. We would also like to capture the wider context of your research and welcome submissions in the following categories: people, science, nature, places, laboratories. The images will be shared throughout 2020 to showcase the work of members and the microbiology community, to introduce other microbiologists and the wider public to your research and the field of microbiology.

We will also launch the Why Microbiology Matters project in 2020, based on the submissions from the microbiology community. We asked the community to submit a nomination for a discovery or event that showcases microbiology and its impact in the past, the present and what current findings could lead to. These areas of research will be published throughout 2020.

I am looking forward to the upcoming Roadshow events in Plymouth and Reading this month, having hosted successful events in Leeds and Newcastle earlier this year, and in Dublin a few weeks ago. I believe some of the best science comes from unexpected collaborations. I hope to encourage as many microbiologists as possible, not necessarily just members, to come together locally to foster new connections, and, with the support of Society staff, encourage more engagement in Society activities. I know from the 2018 Membership Survey that localness is important to the membership and building collaborations is a key element of science research. By attending one of the events you will also enable me to understand what else the Society might be able to do to support you. There will also be further Roadshow events during 2020 as part of our anniversary celebrations and I am looking forward to the opportunity to host these in new locations.

We would also like to welcome more members, from across the UK and Ireland, to take an active role in the Society to help shape what we do. The Society needs your voice and welcomes and encourages members to become Society Champions, submit proposals for Annual Conference and Focused Meetings and consider how they would like to progress their professional development by taking an active role in groups such as the Early Career Microbiologists' Forum.

As my first year as President comes to an end, I have reflected on some of the Society initiatives and events that have enabled me to talk directly with microbiologists to find out more about their work. Being part of these activities has been incredibly enjoyable and rewarding. 2019 has been a significant year, and the Society headquarters has also moved to a new office to allow the Society to better meet the ambitions and needs of the microbiology community. The Society is going from strength to strength and I am looking forward to seeing what the next two years will bring.

Judith Armitage
President
president@microbiologysociety.org

From the Chief Executive

It was a great pleasure at the Microbiology Society's Annual General Meeting to report to the membership about the range of impressive work in recent months. Those efforts are all about strengthening the networks available to the members of the Society, promoting your work and its contribution to society, and making sure that we have robust plans for the future.

Those future plans are ambitious and exciting, and they draw on the Society's core strengths – the experience and knowledge of the members and the professional expertise of the staff. It is this knowledge and expertise, applied in innovative ways, that will allow microbiology to make an ever-bigger contribution to the world around us.

To deliver these ambitions, we need to be better at two things. First, we need to build the strongest possible relationship between the staff and the members, and over recent months and years, we have taken a variety of steps in this direction. Some of these are very obvious, like the President's Roadshow events, where members of the staff team accompany the President around the UK and Ireland to meet directly with members and prospective members. Other initiatives may be less obvious – for example, we have recently brought the administration of the peer review process back in-house for most of our journals. This means that if you need to communicate with someone during that procedure, it will be a member of Microbiology Society staff, who understands the community and the organisation, not someone from an outsourced company.

We are also redoubling our efforts to give a voice to all the different subsets of the microbiology community. The Early Career Microbiologists' Forum has rapidly become established as a vehicle for its constituency to participate in our decision-making. But there are many other ways in which we are moving to empower sections of the microbiology community. For example, our work to help inform discussions about the future strategy of Science Foundation Ireland is, for the first time, giving Irish-based microbiologists a specific and coherent voice in discussions about their future funding opportunities.

The other thing we need to get better at is closing the gap between the Microbiology Society and other groups and organisations who share some of our aims. Some of these will be scientific in nature, and it has been really valuable to build partnerships and joint activities with the Irish Fungal Society, Protistology-UK and the British Yeast Group. But other important organisations will include public bodies, private companies and charities in other sectors. Our project on 'A Sustainable Future' aims to demonstrate the value and raise the profile of microbiology in addressing the world's greatest challenges. It will be most successful where we are able to build common cause with the government agencies and non-governmental organisations that are closest to the work of delivering the United Nations Sustainable Development Goals.

The Microbiology Society has changed a great deal in recent years, and these ambitious aims for the future will mean more change to come. They are not just possible, but also highly successful, because at its core, in its fundamental purpose and its beliefs, the Society has been unwaveringly constant throughout its history. Next year – 2020 – will see our 75th anniversary, and we will collectively celebrate why microbiology matters.

As we do so, it is worth remembering what our far-sighted founders set out to achieve. These were scientific greats like Nobel Laureate Alexander Fleming and Marjory Stephenson, one of the first two women elected to the Royal Society. Time and again, their early meetings stressed the importance of "interconnections" among different microbiologists and the strength that comes from harnessing these links. As we approach our 75th birthday, we live in very different local and global circumstances from those of our founders, but by focusing on the same objectives, the Microbiology Society is well placed not just to celebrate its past but to look forward to an impressive and successful future.

Peter Cotgreave
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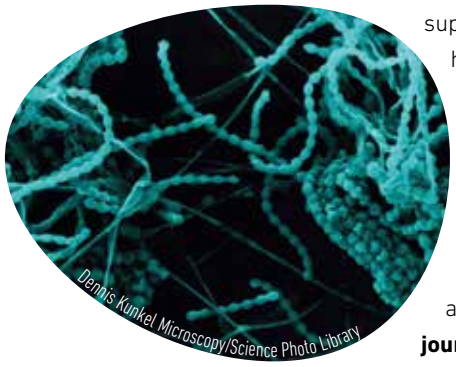
News

New microbiologyresearch.org

The Microbiology Society journals have a fresh new look following an upgrade to the publishing platform in August. The whole Society archive, covering more than 70 years and 60,000 articles, can be found at **microbiologyresearch.org** alongside the very latest content from our six journals.

Our journals are an important part of our mission to advance the understanding and impact of microbiology, both in themselves as places to publish research and through their vital financial contribution to the Society, and member support is vital to their continuing health. You can help by submitting articles, volunteering as a reviewer or editor, or simply letting your institutional librarian know that you value the Microbiology Society journals.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For more information about supporting the journals, email **journals@microbiologysociety.org**.

Society signs Open Access deal with UK Higher Education consortium

With Wellcome Trust and UKRI endorsement, we are excited to announce a new Open Access (OA) initiative between the Microbiology Society and Jisc Collections, the UK Higher Education library consortium.

What does it mean for our UK members?

So long as your university opts-in to our Publish & Read deal with Jisc, articles where you are a corresponding author and which are accepted by any of the Society's six journals will be published OA without further cost to you, your department, your faculty, or your library. At the same time, everyone at your university will be able to read all the paywalled content from the Society's subscription journals.

What about members from outside the UK?

Watch this space. We are discussing Publish & Read deals with other national consortia and with individual university libraries.


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2020 Prize Lectures

We are delighted to announce the 2020 Prize Lecture winners, who will all be presenting at Annual Conference in Edinburgh:

2020 Prize Medal

Professor Martin Blaser
Rutgers University, USA

2020 Fleming Prize

Professor Edze Westra
University of Exeter, UK

2020 Marjory Stephenson Prize

Professor Julian Parkhill FRS
University of Cambridge, UK

2020 Peter Wildy Prize

Professor Graham Hatfull
University of Pittsburgh, USA

2020 Unilever Colworth Prize

Professor Manu Prakash
Stanford University, USA

Harry Smith Vacation Studentships

Applications for support for undergraduate research projects during Summer 2020 will open on 2 December 2019.

Applications should be submitted by the supervisor, and successful applicants will receive support for their research project in the form of a stipend, as well as the chance to apply for a bursary to present the results of their projects at the Annual Conference 2021.

Federation of Infection Societies Conference 2019 (FIS 2019)

11–14 November 2019, EICC, UK

The Microbiology Society is delighted to be hosting the Federation of Infection Societies Conference 2019 (FIS 2019) in Edinburgh between 11 and 14 November 2019.

This event is a unique conference which includes the collaboration of 16 societies across the UK with interests in different aspects of infectious diseases, clinical microbiology, biomedical science and infection control. It provides a great opportunity to find out about the latest developments and to connect with key contacts and networks.

The sessions cover some of the most important current issues facing infectious disease control, prevention, diagnosis and treatment.

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Microbiology Society President could be coming to a location near you

Following on from the successful Roadshow events hosted at the University of Leeds, Newcastle University and Trinity College Dublin earlier this year, this autumn Society President Professor Judith Armitage will continue her journey around the UK and Ireland to engage with members of the Society. You will find Judith at the following locations:

- **18 November** University of Plymouth, UK
- **26 November** University of Reading, UK

Members and non-members are welcome to join these FREE events which unless stated will usually take place between 15:00 and 17:00. There will be the chance to do the following at each event:

- Meet the President, Professor Judith Armitage.
- Engage in interactive, topical discussions.
- Network with local like-minded individuals.
- Find out why microbiology and being part of the Microbiology Society matters.
- Learn how you can get more involved in Society activities, including our 75th Anniversary in 2020.
- Meet the Microbiology Society team.

For more information please contact Erin Taylor at **e.taylor@microbiologysociety.org**.

Grant deadlines

Date	Grant
1 December 2019	Travel Grants for members presenting at conferences from 1 January 2020.
20 January 2020	Society Conference Grants for early career members presenting at Annual Conference 2020. Also, for technicians or retired members and members requiring support for caring costs.
10 February 2020	Harry Smith Vacation Studentships to support undergraduate research projects during summer 2020.

For more information please visit the website (**microbiologysociety.org/grants**).

Connect with the Microbiology Society on social media:

@MicrobioSoc

Gill Elliott

Chair of the Virology Division

The Society has four Divisions (Eukaryotic, Prokaryotic, Virology and Irish) which consist of Society members who support the organisation and plan sessions and symposia for the Society's events programme. Each Division Chair and Chair-Elect sit on the Scientific Conferences Committee and the Chair reports into the Society's governing body, Council. In this article we find out more about Gill Elliott, Chair of the Virology Division.

Gill Elliott

I am Professor of Virology and Research Director in the Department of Microbial Sciences, University of Surrey, UK. My major research interest is the cell biology of herpesvirus infection, primarily of herpes simplex virus. My lab pioneered the development of fluorescent viruses to image virus infection in real time. Viruses are fantastically powerful cell biology tools, and we use them to understand not only the virus in question, but also the cells in which they grow.

When did you first decide you wanted to do science (and why)?

For as long as I can remember I have been fascinated by the world of science – from experimenting with a chemistry set as a ten-year-old to using my brother's rudimentary microscope to look at onion cells. My interest in microbiology began in secondary school, when we learnt about the work of famous scientists such as Louis Pasteur and Edward Jenner. Viruses came much later; in fact, not until my final year undergraduate project at Queen's University Belfast. There I was introduced to the field of molecular virology by my supervisor Bert Rima, and I discovered the joy of research at the bench. I was hooked instantly, and still am.

When did you join the Society and why did you join?

I first joined the Society when I was a PhD student – many years ago! It was a great opportunity to attend a broad-scope conference on a relatively low budget, to hear work presented by top virologists and to network with other PhD students. I always ensure that my own PhD students are able to attend the Annual Conference and experience the same opportunities.

Please describe your role on the Division.

I am currently Chair of the Virology Division. My role is to have oversight of the scientific content of the virology part of the Annual Conference, and to work with my Chair-Elect to co-ordinate the symposia and workshops that the Division organises. I work with a great team of UK and Irish virologists on the Division to come up with stimulating programmes of science, which are delivered by internationally renowned speakers. As Chair of a Division, I also sit on the Society's Scientific Conferences Committee, which brings me into close contact with the other Divisions in the Society and enables me to contribute to the broader decisions made by the committee, helping to shape the conferences in recent years.

Are you a member that would like to join one of the Divisions? Find out more about the Divisions and what they do on our website (**microbiologysociety.org/divisions**). The Council and Committees shadowing scheme (**microbiologysociety.org/shadowingscheme**) is also a fantastic opportunity to gain an insight into the work of the Society and gain first-hand experience of our Council and Committee activities.

Actinomycetes as nature's pharmacists

Lorena T. Fernández-Martínez

Fig. 1. ***Streptomyces coelicolor*** **producing actinorhodin, a blue-pigmented antibiotic.** Edge Hill University photos

The increasing incidence of antibiotic-resistant bacterial pathogens has resulted in an urgent need for new, clinically useful antibiotics. By 2050, antibiotic-resistant micro-organisms are expected to cause more deaths than cancer, road traffic accidents and other chronic diseases worldwide.

This is partly because effective antibiotics are essential to prevent infection when carrying out life-saving medical procedures such as surgery and chronic illness management. While reduction of antimicrobial use in farming and increased antibiotic stewardship are both essential, new viable alternative drugs that can be used in the clinic are still required.

Where do our antibiotics come from?

Soil micro-organisms have always been seen as a great resource for discovering not only antibiotics but also a broad range of other bioactive natural products with antitumoral, immunosuppressant,

antifungal and anthelminthic activity. Amongst soil micro-organisms, actinomycetes are the most prolific producers of bioactive natural products. Actinomycetes are ubiquitous bacteria and, as such, they can be found in most environments on Earth.

Streptomyces were the initial antibiotic makers

Most of the antibiotics used in medicine and veterinary settings are produced by actinomycetes, a fascinating group of non-motile filamentous bacteria. The most prolific producers of antimicrobial compounds, responsible for the production of over two-thirds of these clinically relevant molecules, belong to the genus *Streptomyces,* which is abundant in all soil environments. During the period from 1950–1970, known as the Golden Age of antibiotic discovery, soils were intensely screened by the pharmaceutical industry in order to isolate antibiotic-producing micro-organisms including mostly *Streptomyces* species and other closely related actinomycetes genera. This approach resulted in thousands of drugs being identified during this period, and later applied to the clinic, including a variety of antimicrobial compounds. However, after just a couple of decades, rediscovery of specialised metabolites became a regular occurrence and the rewards from this type of strategy were substantially reduced.

Screening new environments could lead to the discovery of new antimicrobial compounds

Screening similar environments in search of actinomycetes tends to lead to the isolation of micro-organisms which produce structurally similar antibiotics. This has encouraged scientists in the natural product discovery field to start exploring more unusual environments in the hope that novel strains containing new antibiotic gene clusters with potential clinical use will be identified.

In recent years, the astonishing diversity of natural products from actinomycetes found in marine environments has become apparent. Over 250 novel bioactive compounds have been reported from approximately 100 different actinomycete strains, belonging to nearly 40 different genera, in the last decade. Among them, genera such as *Salinispora,* with over 40 novel compounds identified including the medically relevant salinosporamides; *Verrucosispora,* with 18 new compounds identified including the abyssomicin family of antibiotics; *Nocardiopsis* (52 new compounds) and *Micromonospora* (46 new compounds) are showing remarkable potential as sources of structurally diverse, novel, specialised metabolites with both unique chemical moieties and clinically relevant activities.

The Atacama Desert of northern Chile, considered to be one of the most arid and extreme environments on Earth, has also proven to be an unexpectedly rich resource of actinobacterial and novel chemical diversity. A total of 46 secondary metabolites representing diverse chemical classes including alkaloids, peptides, macrolides, terpenes and polyketides such as the novel antimicrobials chaxalactins and chaxamycins, are derived from only a few *Streptomyces* strains isolated so far from that environment.

Actinobacteria associated with the cuticle of different species of leafcutter ants have been identified in recent years as extraordinary reservoirs of bioactive molecules which assist leafcutter ants in protecting their fungus gardens against a diverse array of natural enemies, most of which are fungal pathogens. Examples of talented actinomycetes, in terms of specialised metabolite diversity, isolated from leaf cutter ants to date belong to genera such as *Rhodococcus*, *Nocardia*, *Microbacterium*, *Kitasatospora*, *Pseudonocardia* and *Streptomyces* such as *Streptomyces formicae* KY5, producer of a group of pentacyclic polyketides known as formicamycins which present antibacterial activity against multidrug-resistant strains.

This is only a small sample of the chemical diversity of bioactive specialised metabolites encoded in the genomes of actinomycetes isolated worldwide to this point.

Increasing yield is essential in order to produce a successful drug candidate

The development of improved next generation sequencing and mass spectrometry technology, as well as bioinformatic programmes able to identify specialised metabolite biosynthetic gene clusters has emphasised the vast genetic potential of actinomycetes as nature's pharmacists. In fact, their potential to produce specialised metabolites is far more than initially revealed by traditional screening.

In order for any promising bioactive compound to undergo clinical trials, it is critical to obtain high enough levels of the drug. The challenge most actinomycetes geneticists face is to find efficient ways to increase the yield of these potential candidates, particularly those compounds for which biosynthetic gene clusters are encoded in the genome but production levels are barely detectable under laboratory conditions.

Based on their genome sequences, most actinomycete species have the

potential to produce on average around 10–15 antimicrobial agents of natural product origin. However, when these species are grown under laboratory conditions, only one or two antimicrobial compounds are usually detected. This is because most of these antibiotic gene clusters appear dormant (i.e. are not expressed) under laboratory conditions. The fact that actinomycete species maintain these intact antibiotic gene clusters in their genomes suggests the products are useful in nature, probably to attack competitor micro-organisms in their harsh environments. These dormant or cryptic antibiotic gene clusters represent an untapped resource in terms of novel chemistry which could lead to the discovery of new antimicrobial compounds that could be very useful in the clinic if we were able to produce them in high enough amounts.

There are several ways in which scientists can 'awaken' and increase production of these silent gene clusters. One of these key approaches is to understand the regulation of specialised metabolite gene clusters. By growing actinomycete strains under conditions similar to those they would encounter in their natural environment, scientists can understand the signalling pathways leading to the expression of these compounds and later manipulate them in the laboratory. Identifying the role of regulatory proteins ultimately controlling the production of a novel antimicrobial compound allows scientists to manipulate biosynthetic pathways using a rational approach; i.e. overexpression of positive regulators and/or deletion of negative regulators from the genome, hopefully leading to increased yield of the compound. The recent development of actinomycete genetic tools which

Fig. 2. **Actinomycetes isolates from soil samples worldwide.** Lorena Fernández-Martínez.

generate clean deletions of genomic regions such as the SceI meganuclease system and the pCRISPomyces plasmids have considerably facilitated this task.

Another tactic to enhance production of specialised metabolites involves increasing the availability of precursors in the media so as to encourage induction of biosynthetic gene clusters, and finally, cloning entire biosynthetic gene clusters into heterologous hosts has also proven successful. Heterologous expression has the advantage of removing global transcriptional ties present in the natural producer, but good understanding of the metabolic resources and regulatory cascade required for the production of these 'silent' pathways in the natural producer also needs to be considered in order to successfully obtain high yields of the compound of interest.

Future perspectives

Actinomycetes are ubiquitous nature's pharmacists which provide us with a plethora of novel bioactive compounds to be explored. It is through interdisciplinary collaborations and innovative ideas that we will continue to unlock their potential and keep ahead on the antimicrobial resistance arms race.

Further reading

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edgehill.ac.uk/biology/research/actinomycetes-biology-antibiotic-discovery

Lorena Fernández-Martínez studied a BSc in Genetics and Biochemistry before completing a PhD on the regulation of stress responses in the bacterial genus *Streptomyces*. She then moved to postdoctoral positions at INBIOTEC, Spain and John Innes Centre, UK. Her research at Edge Hill University focuses on understanding the complex regulatory pathways that lead to specialised metabolite production in actinobacteria by using gene manipulation, co-cultivation and environmental extracellular signalling methods. Lorena has been a member of the Microbiology Society for 17 years.

Why does microbiology matter?

Micro-organisms are essential for life on Earth. Understanding microbiology helps us understand environmental and ecological interactions on the planet, the evolution of living organisms, plant and animal health (including humans), as well as providing biotechnological solutions to current problems. That's why all aspects of microbiology are so important and worth studying.

What is the best career decision you have ever made?

I think one of the best decisions in my career was joining the Microbiology Society Communications Committee, as it has given me the opportunity to meet fantastic people working in completely different aspects of microbiology, who are now friends and collaborators.

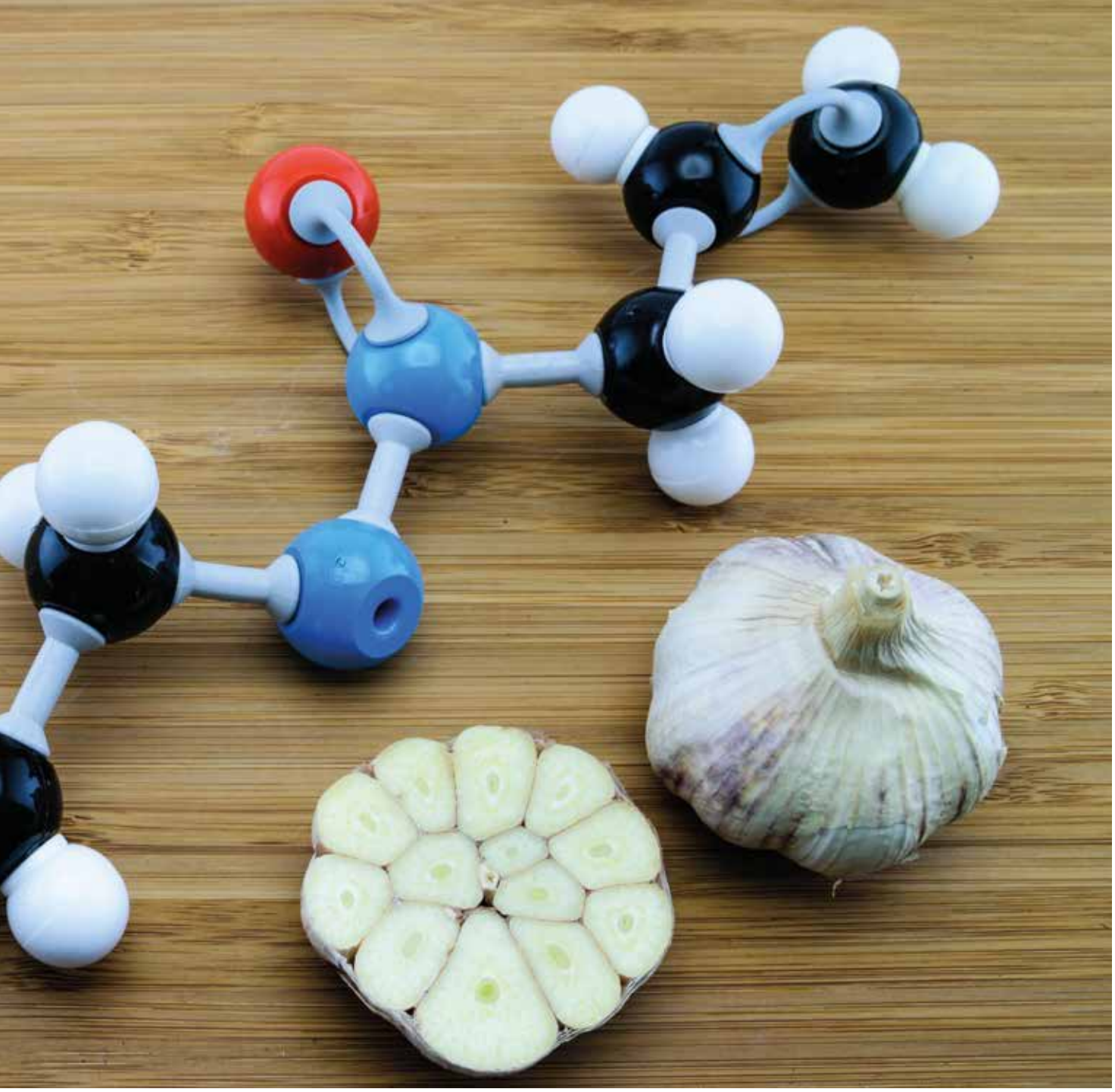
Breaking barriers with garlic

Almost every day there is another news headline calling for new, effective and affordable treatments for many of the diseases that are prevalent in society. Non-communicable diseases such as ischaemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), respiratory cancers and diabetes have been named as diseases needing new treatments.

Heather Graz

Infectious diseases such as lower respiratory tract infections and tuberculosis are also highlighted in public health literature as leading causes of death, for which new and more effective treatments are needed if the effects of global health crises, such as antimicrobial resistance, are to be circumvented.

The reported health benefits of garlic are wide-ranging and touch on many of these diseases, including cancer, cardiovascular disease and infectious disease. On first thought, this apparent alignment between a problem and a possible solution sounds like a cinch. But do these reports of garlic's health benefits stand up to scientific scrutiny so that we can use them as part of a solid evidence base for developing new treatments? And if so, what needs to be considered to transform a lowly clove of garlic into a credible, pharmaceutical intervention



Molecular model of allicin. topthailand/iStock

that complies with the drug development standards of modern-day healthcare?

The drug development process

A starting point to answer these questions lies in the nature of contemporary accepted drug development processes and in an understanding of how natural products and their processing relate to these requirements (Fig. 1).

Basic research and discovery

Early drug development starts when, during hit identification stages, compounds are identified that show potential to act upon a particular symptom or disease. These hits are refined and improved during subsequent hit optimisation, hit-to-lead and lead optimisation experimentation stages, yielding compounds that can be selected to be taken into more in-depth and expensive pre-clinical studies. This *in vitro* work is carried out in laboratory settings and starts to shed light on if and how compounds may work.

In garlic, as in most other natural products, numerous interacting compounds are present in varying amounts across samples. This translates into a likelihood that a given compound may exhibit several interrelated mechanisms of action. For long-term scientific research, this holds much promise. In current drug development

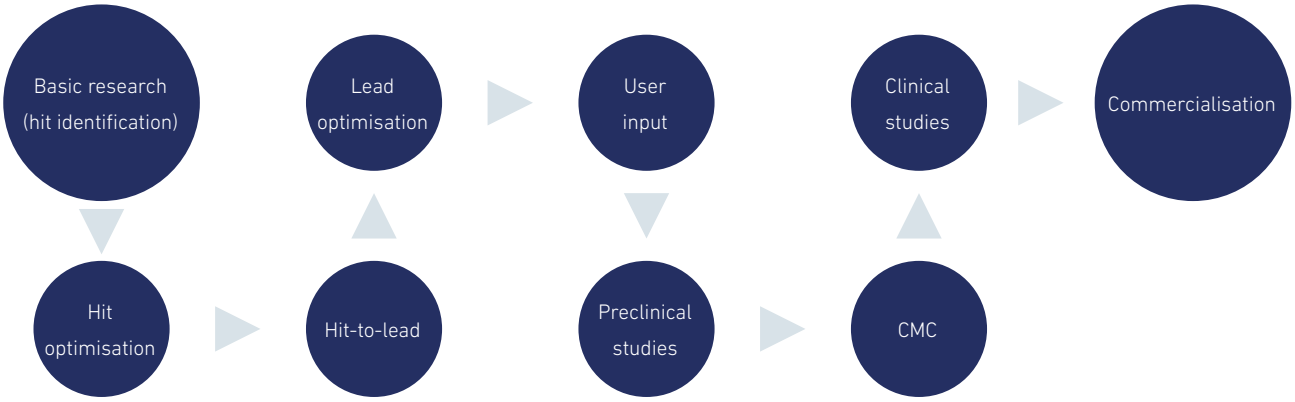


Fig. 1. **Sequence of stages in the contemporary pharmaceutical drug development process.** Heather Graz

practice, it complicates the process of isolating a specific target compound for further testing and generating repeatable and acceptable data for regulators.

While some advances have been made in understanding some of the mechanisms by which garlic exerts its influence, large gaps in our knowledge remain about how its complex and multifaceted chemistry works with other chemistry and in biological systems. This is key in being able to refine the design of subsequent experiments and strengthen one's data package. Innovative technologies and techniques such as fluorescence imaging, high-throughput screening, microfluidics and computational chemistry advances are helping to bridge these gaps.

Although not universally done, it is always better to seek feedback from end-users of the envisioned end product. Early discussions with patients and clinicians help to avoid wasting time and money on developing a product that people will not use. With garlic, this is even more important. Garlic evokes strong emotions – people either love it or hate it – so concerns about odour or taste have to be addressed.

Pre-clinical studies

During the pre-clinical stage, data on dosing, metabolism of the compound and the compound's toxicity is generated for use in clinical studies. Dosage is key when working with garlic, to avoid the corrosive and toxic effects that the bioactive compound allicin and its degradation product, ajoene, can have.

The question of how to get enough of the active molecule into the right place in the human body is another vital consideration. As it is originally of plant origin and a source of food for humans, garlic's health-inducing compounds, such as allicin or ajoene, are easily and quickly broken up by the human body. This means that limited amounts of the compounds remain for long enough to be able to be taken up by the body and harnessed for medicinal purposes. This introduces a conundrum of balancing volume, concentration of bioactive molecules and the best delivery mechanism to achieve the best effect, without causing adverse effects. This is as much an art as it is a science to develop a pharmacologically active dose.

Chemistry, manufacture and controls

Chemistry, manufacture and controls (CMC) ensure that adequate amounts of optimised and approved compound are manufactured for use in upcoming clinical studies. This requires know-how in scaling up, from lab-scale experiments into commercial production. Robust and regulated quality assurance and control processes need to be in place.

Key issues to consider during CMC include how best to formulate your compound for delivery and uptake in humans. This is particularly important when working with garlic, as its active compounds break up and degrade easily when they come into contact with mammalian tissue, limiting bioavailability of the targeted compound.

Economic factors such as cost per dose administered and ease of manufacture also come into play here. Conversion of natural product extracts into druggable compounds is often complex and costly and it may therefore not make business sense to proceed.

Clinical studies

This stage evaluates the safety and efficacy of the compound in a human

body rather than in a test tube. This is key as it opens the door for further product development and commercialisation.

Medicinal regulatory authorities globally are, however, often hesitant to accept medical interventions that are based on natural products. Variable amounts and concentrations of bioactive compounds across testing and manufacturing batches make it difficult to obtain repeatable results during development. Multiple mechanisms of action also reduce the ability to explain a single compound's mechanism of action unequivocally. In practice, this means that there are no accepted processes for guiding development of natural products that are readily available to regulators, potentially requiring developers to carry out more extensive testing and increasing the cost of a compound's development.

For many companies, such increased cost could make the difference between success and failure to achieve drug approval with their compound.

Advances in microbiological, chemistry and data science technologies may offer scope to strengthen this evidence base and break new ground in our understanding of garlic's chemistry and biology interactions and potential for druggability.

A way forward?

So, can garlic be developed into an approved medical intervention for animal or human use? Conventional wisdom would suggest that at least at conceptual level, this should be possible, at some point in time.

We are not starting from a strong evidence base, however, with lack of detail about the compound composition of garlic extracts used, variations in rigour of experimentation processes and short duration of studies being common criticisms of many of the studies that have looked at garlic's health effects.

From a glass-half-full perspective, perhaps the answer lies in asking a better question. Advances in microbiological, chemistry and data science technologies may offer scope to strengthen this evidence base and break new ground in our understanding of garlic's chemistry and biology interactions and potential for druggability. Perhaps the question needs to be whether developing garlic as a medicine can be part of a broader innovation in a science–business–healthcare triad. Now that would be a high-impact breakthrough.

Further reading

Block, E. *Garlic and Other Alliums. The Lore and the Science*. Cambridge: Royal Society of Chemistry; 2010.

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Heather Graz has an MBA from Exeter University and before that almost 25 years of experience in direct patient care and business management. She transitioned into the biotechnology sector and has been responsible for managing commercial aspects of plant-based drug development for the past five years.

What advice would you give to somebody starting out in the field of pharmaceutical drug development?

Pharmaceutical drug development is a high risk but potentially high-impact field. It is complex and fascinating, and we are all only one cog in a very large machine. Be willing to start at the bottom, keep an open mind and learn as much as you can from the experienced people around you. Above all, remember to keep the patient, who will benefit from a successful treatment, at the forefront of what you do. They are the ultimate reason that we do what we do.

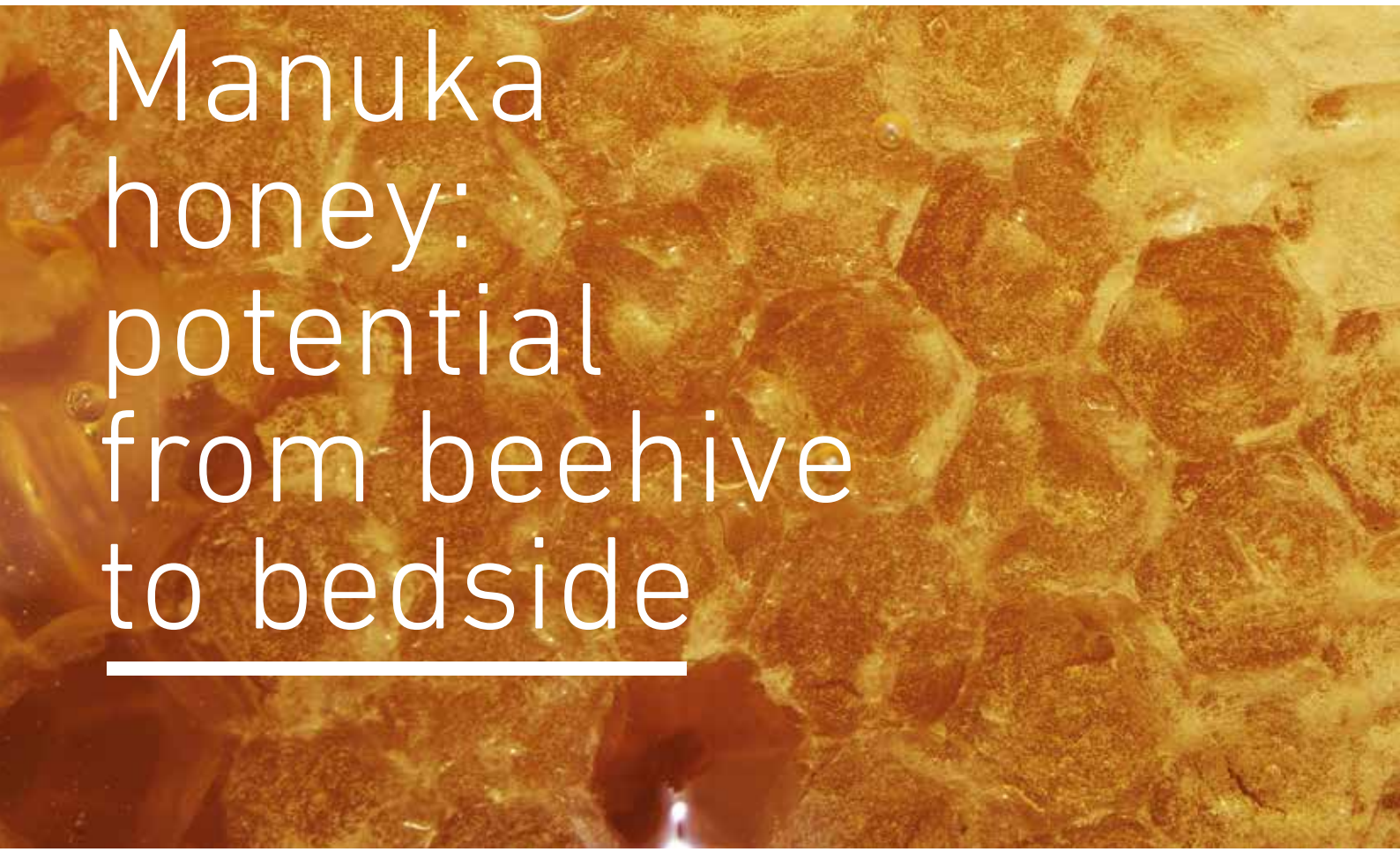
What is your greatest achievement to date?

Learning a completely new business skill set as a mature student and merging this with 25 years of prior direct patient treatment experience in a career transition from frontline speech and language therapy to managing commercial aspects of novel drug development in the biotechnology industry.

Antibiotics have been a cornerstone of medical treatment since they were first introduced in the 1940s. They've allowed transmissible infections to be treated and opened up the possibility of more invasive medical procedures. However, the impending antimicrobial resistance crisis is set to undo all of this. In a post-antibiotic era, can manuka honey, a natural product with a successful past, undo this sticky situation?

Aled Roberts

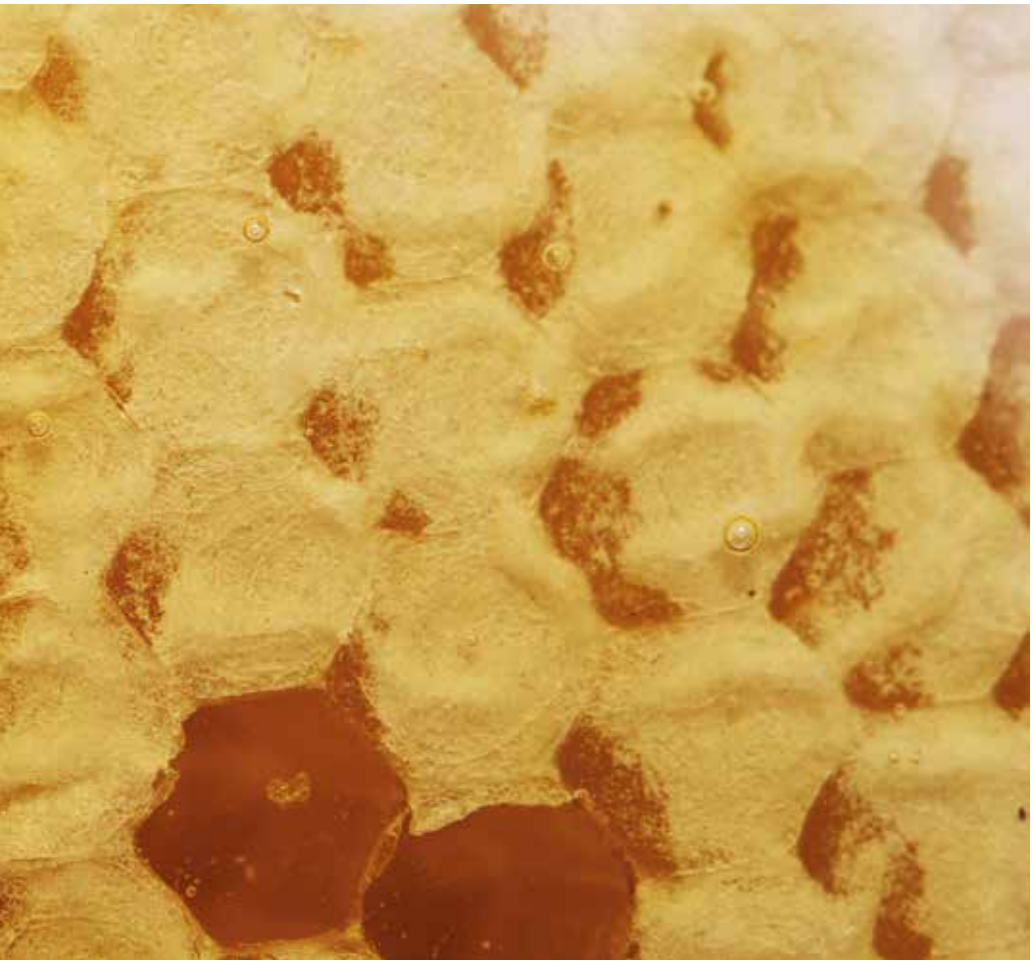
Manuka honey: potential from beehive to bedside



Sticky situation surrounding antimicrobial resistance

The emergence of antimicrobial resistance (AMR) was all but prophesised by Alexander Fleming in the 1940s following the clinical introduction of penicillin, and by the late 1990s and early 2000s the downfall of 'Big-Pharma's' antibiotic drug discovery pipeline was all but certain. Too few people outside of academic circles took note and the wider community was unaware until the tireless work of Dame Sally Davies and Lord Jim O'Neill. Together they have painted bleak futures for our children which has since put the impending AMR crisis at the forefront of science policy and political debate within the UK. Now, we are regularly reminded in some form or another of the impending AMR crisis (and quite rightly so!). More recently, small biotech companies and academic researchers alike are pursuing the antibiotic mantle once held by 'Big-Pharma', searching for the next generation of antimicrobials in the most unlikely places. One such place gaining increased interest of late is the beehive, and more specifically, the honey contained within. As a natural product made from the constitutes of its surroundings, there are many different types and, more recently, the medicinal properties of these have been investigated.

Manuka honeycomb. welcomia/iStock



So, is all honey created equally?

Well yes and no. Honey is a natural product with a complex chemistry that contains up to 600 unique compounds. However, 97% of its weight is made up from four simple sugars (fructose, glucose, maltose and sucrose) and water. These 'non-variable' components are consistent across all honey types, giving rise to the characteristic sweetness and self-preserving qualities. The sugars achieve this by reducing the pH and water activity of the honey to a level where growth is prohibited, but this antimicrobial effect is short lived when the honey becomes diluted. The remaining 3% is a 'highly-variable' mixture of minerals, oligosaccharides, organic acids, phenolic compounds, proteins and vitamins which are produced by plants and incorporated into the nectar (along with the sugars). Therefore, the exact cocktail of compounds present within a honey is representative of the botanical source (and growth conditions) from which the nectar was gathered, giving rise to honeys with distinctive tastes, colours, and aromas.

More importantly (at least in the context of this article) these botanical compounds can increase the overall antimicrobial activity of the honey, even when it becomes diluted. This increased antimicrobial activity is not a certainty and has led to the identification of some honeys that are more potent than others, gaining them notoriety within the field. Manuka is one such honey that was identified in the mid 1980s as having

exceptional antimicrobial activity that was retained upon extensive dilution. This activity is due to the incorporation of manuka bush botanics into the honey. One key compound is methylglyoxal, which is derived from dihydroxyacetone in the starting nectar. It is believed that this is responsible for the majority of manuka honey's antimicrobial activity and the evidence suggests there are other as yet unknown compounds that modulate activity.

Inhibitory effects to unstick the AMR crisis?

Recently, researchers have tried to better understand the antimicrobial activity of manuka honey, identifying the mechanism by which it inhibits bacterial cells and the compounds responsible for this activity. Two distinctly different mechanisms have been identified to date against two unique bacterial species. Against *Staphylococcus aureus*, a notorious Gram-positive nosocomial pathogen, manuka honey arrests the latter stages of the cell division process (post septa-formation between daughter cells) resulting in the death of daughter cells. Conversely, against *Pseudomonas aeruginosa*, an inherently difficult to treat Gram-negative pathogen, manuka honey destabilises the cell envelope (down-regulating cell wall anchor proteins) leading to membrane blebbing, which eventually results in cell lysis. It is unclear if these mechanisms are finite, representing species-specific interactions, or if they form a broader inhibitory action that is Gram-specific. What is certain is that manuka honey has the ability to inhibit a wide range of clinical pathogens such as *Acinetobacter, Burkholderia, Enterococcus, Listeria, Salmonella, Shigella* and *Streptococcus* species, even though the mechanism against them remains unclear. Importantly, these inhibitory effects are not confined to planktonic culture, with observable inhibitory effects seen against biofilms and chronic *in vivo* infections. As a product with broad-spectrum activity, it makes an excellent candidate for the initial treatment of infections, particularly where the exact causative agent isn't known immediately. Even when manuka honey is diluted beyond its inhibitory concentration, it still retains some activity, attenuating a wide range of virulence traits in various bacterial species.

Manuka flower. purefocus/iStock

Is the future bright, is the future golden?

The majority of these effects have been observed *in vitro*. However, there

For manuka honey at least, all previous *in vitro* attempts to generate resistance have been unsuccessful ... and there are currently no reports of *in vivo* resistance, most likely due to the presence of multiple selection pressures from a wide range of botanical compounds exerting some effect.

is a clear need to design robust *in vivo* clinical trials and build upon growing anecdotal evidence and small *in vivo* case studies. One of the biggest hurdles which currently limits its clinical applicability is the effective delivery of manuka honey to the infection site. While this is of limited concern in surface wounds (which popularised the clinical use of manuka honey in the first place), it becomes increasingly tricky to deliver manuka honey at effective concentrations within the body. Developing novel delivery mechanisms or incorporating manuka honey into pre-existing clinical products may aid its clinical transformation. For example, *in vivo* studies have suggested that its incorporation into sino-nasal wash solutions can improve culture negativity in chronic rhinosinusitis patients, while *in vitro* combinational therapy has proven successful against many bacterial species. Various studies into combinations of antibiotics and manuka honey have shown that it can help some antibiotics overcome resistance mechanisms to the point where they become effective once again.

Regardless of any headway we make in antimicrobial research going forward, if antimicrobial resistance is soon to follow then any progress is futile. It is therefore crucial that future antimicrobials are vigorously tested for their ability to generate spontaneous resistance among clinical pathogens. For manuka honey at least, all previous *in vitro* attempts to generate resistance have been unsuccessful (although increased tolerances by biofilms have been reported) and there are currently no reports of *in vivo* resistance, most likely due to the presence of multiple selection pressures from a wide range of botanical compounds exerting some effect. As we understand it today, this complex chemistry is key to its broad-spectrum activity, anti-biofilm effects and virulence attenuation. It is clear that the future for manuka honey is looking bright as we move ever closer to elucidating additional mechanistic effects, identifying additional novel compounds within manuka honey that have therapeutic significance and push manuka honey into a clinical setting via *in vivo* testing. Only time will tell if it is golden.

Aled Roberts

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Aled Roberts is a Hodge Foundation-funded Postdoctoral Researcher in Dr Rowena Jenkins' laboratory. He completed a PhD detailing the mechanistic effects of manuka honey on *Pseudomonas aeruginosa* and his current research interests focus on the potential use of natural products to combat antimicrobial resistance in multiple human pathogens.

What skills are required in your position on a day to day basis?

A range of skills are required to complete my job, from aseptic techniques to the use of specialised equipment. However, one of the most widely used skills is that of patience, especially when things start going wrong!

What do you do in a typical day/week?

A typical week for me includes planning and conducting various experiments in the lab, and if they don't work (which they inevitably don't), I have to troubleshoot the problems and find a solution. The rest of the week is filled with paperwork, reading and, most importantly, coffee!

Burkholderia bacteria: natural alternatives to synthetic pesticides

Alex J. Mullins and Eshwar Mahenthiralingam

Micro-organisms have fascinating lifestyles and many of those that live in the natural environment carry out beneficial or detrimental functions depending on the situation in which they find themselves. Gram-negative *Burkholderia* represent one group of bacteria with exactly these 'Dr Jekyll and Mr Hyde' tendencies.

The major negative effect *Burkholderia* are known for is infection within a range of hosts including humans, animals and plants; in contrast, they also mediate highly beneficial interactions. A timeline of these positive and negative traits, together with key landmarks in our understanding of *Burkholderia* are shown (Fig. 1). Here we expand on how the dilemma of inherent *Burkholderia* pathogenicity initially led to a decline in the exploitation of these bacteria as beneficial biopesticides in the 1990s. However, renewed interest in these bacteria as a source of natural products and antibiotics, coupled with a greater understanding of their diversity and genomics, has provided an opportunity to repurpose *Burkholderia* as safe biopesticides (Fig. 1).

Burkholderia bacteria are diverse!

The evolutionary history of *Burkholderia* bacteria continues to be unravelled with the ongoing discovery of novel species and regular updates to the taxonomic distinction between genera. From their initial discovery in 1952 as the cause of onion rot, *Burkholderia* bacteria were associated with pathogenicity. The majority of research on these bacteria has focused on understanding the species most associated with disease (Fig. 2): the *Burkholderia pseudomallei* group as primary pathogens; the *Burkholderia cepacia* complex as opportunistic pathogens well known for causing lung infections in people with cystic fibrosis (CF); and the *Burkholderia gladioli* group of plant pathogens. However, all *Burkholderia* are capable of living freely or as symbionts in the natural environment, and are not always found associated with infection.

Recent taxonomic analysis has split *Burkholderia* further, defining the novel genus *Paraburkholderia* (Fig. 2). *Paraburkholderia* species are rarely encountered as pathogens and hence some researchers have referred to them as the environmental or beneficial group. But this is an oversimplification as certain *Paraburkholderia* species can cause opportunistic human infections, nearly all *Burkholderia* and *Paraburkholderia* occur widely in the

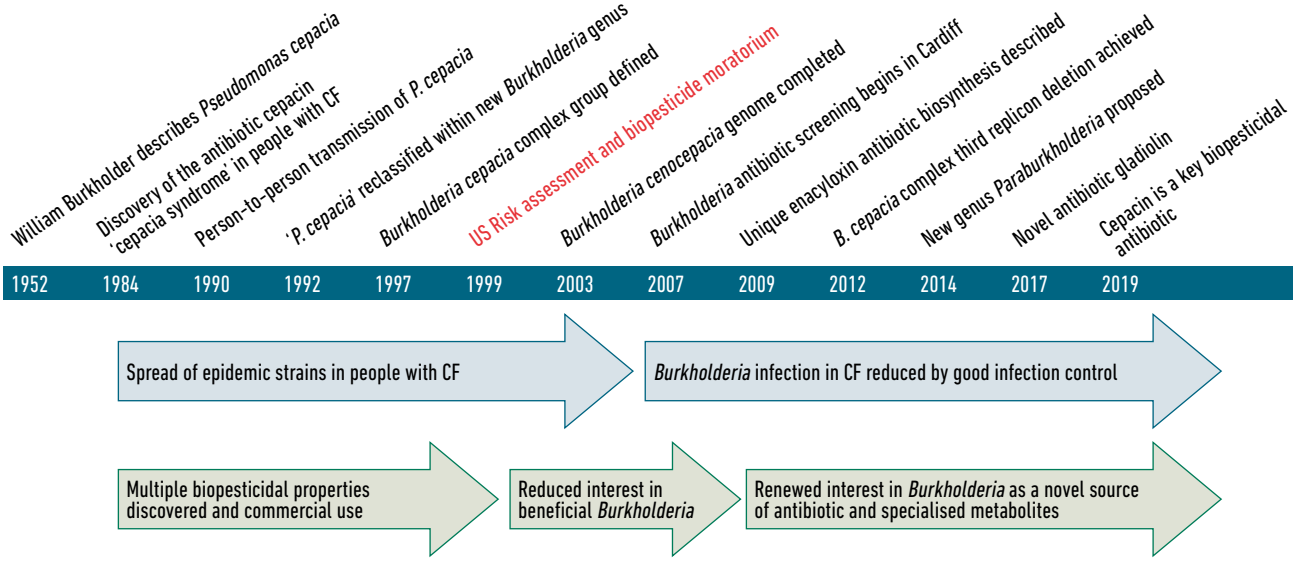

Fig. 1. **Key events in our understanding of *Burkholderia* bacteria as both pathogens and beneficial bacteria. A basic timeline from the discovery of these bacteria to current research on how they work as biopesticides is shown.** Eshwar Mahenthiralingam and Alex Mullins

natural environment, and finally, multiple beneficial interactions have been characterised for both groups.

Burkholderia produce multiple specialised metabolites

The ability to antagonise and kill a range of other micro-organisms was a key feature that drove the initial exploitation of *Burkholderia* bacteria as biopesticides. Although a number of antibiotics such as cepacin (Fig. 1) were historically known to be produced by *Burkholderia*, recent genomic analysis has shown that they encode multiple biosynthetic gene clusters for the production of various specialised metabolites. *Burkholderia* can produce polyketide antibiotics (e.g. enacyloxin and gladiolin; Fig. 1) that are made by large, modular biosynthetic gene clusters. They can also make both ribosomally synthesised and post-translationally modified peptides (e.g. capastruin) and non-ribosomally synthesised peptides and lipopeptide antibiotics (e.g. icosalides). The use of genome mining to identify novel biosynthetic gene clusters combined with sensitive analytical chemistry greatly enhances specialised metabolite discovery in *Burkholderia* bacteria.

Large unusual genomes and a non-essential third replicon

Given their functional diversity, it is not surprising that *Burkholderia* also have very large genomes to encode these multiple capabilities. Their genomes are nearly twice the size of most bacteria, ranging from six to nine million base-pairs of DNA. *Burkholderia* also represent a minority of bacteria that package their genomes into multiple large replicons instead of having just one chromosomal piece of DNA. The majority of *Burkholderia* and *Paraburkholderia* species have two-replicon genome structures. The *Burkholderia cepacia* complex group of species (Fig. 2) have a three-replicon genome. In 2012 (Fig. 1), it was found that the *Burkholderia cepacia* complex third replicon was not an essential piece of DNA and could be genetically removed. Third replicon mutants lost a number of functions, including the production of antifungals and, most strikingly, their virulence in a range of infection models.

Burkholderia biopesticides

Multiple chemically synthesised pesticides are used to protect crops against a range of pathogens and during vulnerable stages of their growth. Germinating crop plants are highly prone to attack by pathogens, with damping-off disease (the failure of seeds to germinate or rapid wilting of recently

***Burkholderia cepacia* complex group**
- More than 20 species
- *B. multivorans* & *B. cenocepacia* prevalent in CF
- Commercially exploited as biopesticides

***Burkholderia pseudomallei* group**
- Tropical disease melioidosis
- *Burkholderia mallei* causes glanders in horses
- Potential bioterrorism agents

***Burkholderia gladioli* group**
- Includes *B. glumae* & *B. plantarii*
- Cause multiple plant diseases including mushroom rot and rice blight

New *Paraburkholderia* group
- Mainly environmental
- Certain species can cause opportunistic infection
- e.g. *Paraburkholderia fungorum*

Fig. 2. **Example species and the properties of different groups of *Burkholderia* bacteria. The four groups of *Burkholderia* currently being studied by researchers and example species within them are shown.** Eshwar Mahenthiralingam and Alex Mullins

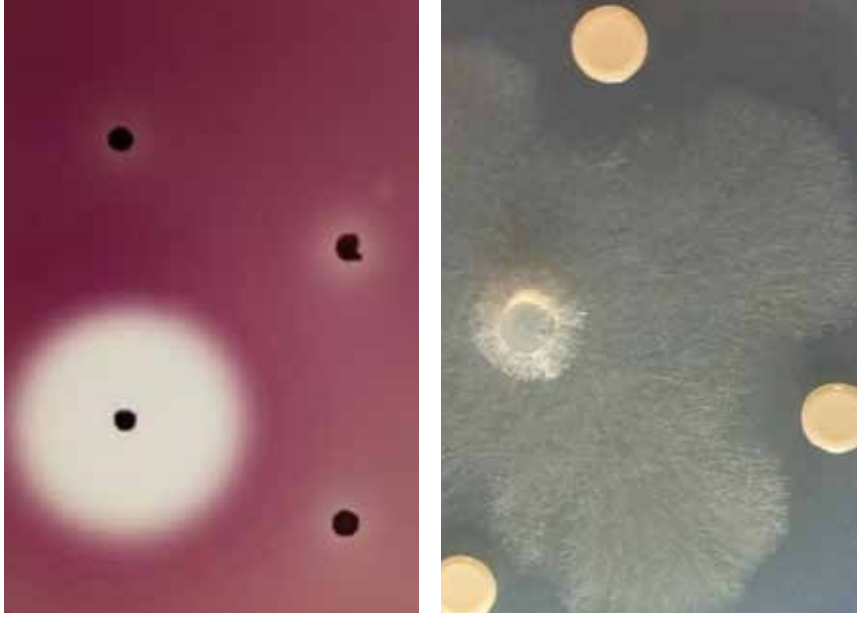

Fig. 3. **The antimicrobial activity of *Burkholderia ambifaria*.** Antagonism against the Gram-negative *Pectobacterium* is shown as a zone of clearing around a black, antibiotic-producing *Burkholderia* colony (left) and inhibition of the filmentous growth of the oomycete damping-off pathogen *Pythium* by 3 *Burkholderia* colonies (right). Alex Mullins

emerged seedlings) caused by a range of fungi and fungal-like organisms called oomycetes. During the 1990s, several *Burkholderia* biological control products were registered with the US Environmental Protection Agency (EPA) and used successfully in a range of applications, including protection against damping-off disease.

Products, including Deny® and Blue Circle® manufactured by Stine Microbial Products, were described as containing [*Burkholderia cepacia*] strains M54 and J82. These strains and multiple other isolates with biocontrol properties were subsequently identified as the species *Burkholderia ambifaria*. In parallel with this beneficial use as biopesticides, [*Burkholderia cepacia*] bacteria were also emerging as devastating CF pathogens (Fig. 1). In 1999, after assessing the risks of *Burkholderia* biopesticides, a moratorium was placed on the registration of all new biopesticides until they could be proven safe (Fig. 1).

Cepacin is a key biopesticidal *Burkholderia* metabolite

In 2015 we began a genome mining study to find out which specialised metabolite biosynthetic gene clusters were encoded and expressed by biopesticidal *Burkholderia ambifaria* strains. We found that *Burkholderia ambifaria* strains encoded at least 38 different specialised metabolite biosynthesis gene clusters and had a broad range of antimicrobial activity (Fig. 3). We also identified a novel gene cluster controlled by the bacterial signalling system quorum sensing that, when mutated, stopped *Burkholderia ambifaria* from producing the historical antibiotic cepacin.

The *Burkholderia ambifaria* biopesticidal strains had been shown to protect crop plants such as peas against damping-off disease caused by *Pythium*. Simply coating pea seeds with the *Burkholderia ambifaria* enabled protection when they were planted in pathogen infested soil (Fig. 4). When the same biocontrol assay was carried out with the *Burkholderia ambifaria* cepacin mutant protection was lost. We also generated a *Burkholderia ambifaria* third replicon mutant which, despite the loss of nearly 1 million bases of DNA, still had a functional cepacin biosynthesis gene cluster. The third replicon mutant still gave excellent biocontrol protection of peas but crucially when tested in a mammalian infection model it had lost its pathogenicity and ability to persist.

Fig. 4. **Biopesticidal protection of peas by *Burkholderia ambifaria* in soil infested with *Pythium*.** Pea seeds were planted in soil infested with the damping-off pathogen *Pythium* and as a result failed to germinate (left), coated with *Burkholderia* and germinated successfully when planted in the same infested soil due to protection from antimicrobial cepacin production (centre), and planted in un-infested soil where they germinated successfully (right). Alex Mullins

Future perspectives – what is needed to allow safe use of *Burkholderia* as biopesticides?

It is now clear that *Burkholderia* represent a novel source of antibiotics and encode a huge diversity of specialised metabolite biosynthetic gene clusters. To fully harness the potential of *Burkholderia* as natural biopesticides, we have to find out exactly how they work, for example as we have done by uniquely linking cepacin production to protection against *Pythium* damping-off disease. We also must find out what happens to biocontrol strains when they are applied to crops and left in the field environment. To

be environmentally safe they need to decline naturally, and not build up or interfere with other microbial systems that maintain soil health.

Most importantly we need to make sure any *Burkholderia* biopesticides will be safe for use and will not cause infection. This can be done via an attenuation strategy; for example, removing the third replicon greatly reduced *Burkholderia ambifaria* pathogenicity, and now with modern strategies to develop safe bacterial vaccines, we can also consider removing other infection-mediating genes from biocontrol strains. Commercial confidence in the potential of *Burkholderia* biopesticides also appears to be re-emerging in the US, with Marrone Bio Innovations® marketing heat-killed *Burkholderia* products possessing nematocidal and mitocidal properties. Overall, producing enough food to feed the growing human population is a major global challenge, and this needs to be balanced against the environmental impacts of intensive agriculture. *Burkholderia* and other natural microbial biopesticides, which will not impact the environment, have huge potential to help sustain future agricultural production.

Acknowledgements

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Further reading

Mullins AJ, Murray JAH, Bull MJ, *et al.* Genome mining identifies cepacin as a plant-protective metabolite of the biopesticidal bacterium *Burkholderia ambifaria*. *Nat Microbiol* 2019;4:996–1005.

Alex J. Mullins

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Alex J. Mullins graduated from Cardiff in 2015 with a BSc in microbiology, having written his dissertation on *Burkholderia* bacteria in the Mahenthiralingam Lab. He decided to pursue this research further and started a PhD, investigating the genomic and antibiotic properties of the historical biopesticide *Burkholderia ambifaria*. Following his PhD, he continues to research *Burkholderia* as a postdoctoral researcher.

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After completing a degree in Applied Biology at Cardiff and a PhD with the Medical Research Council, **Eshwar Mahenthiralingam** carried out 10 years of postdoctoral research on cystic fibrosis at the University of British Columbia, Canada. He joined Cardiff University in 1999. In addition to teaching microbiology and guiding his research group, he is also Co-Director of Research and works on the school's management team.

What inspired you to become a microbiologist?

Alex: I became interested in microbiology at school when we learnt about major historical diseases such as bubonic plaque and the role of microbes in vital nutrient cycles such as nitrogen fixation. I saw so much potential in these organisms that you could not see and, inspired by a biology teacher with a degree in microbiology, I followed up by studying and now researching microbiology at university.

What skills are required in your position on a day to day basis?

Eshwar: When I was training as a microbiologist, the key skill areas I developed were in molecular biology and genomic analyses, and these, combined with bioinformatic knowledge, are now crucial for many areas of microbiology. Other key research skills include perseverance, curiosity, and the confidence to take risks and occasionally do 'whacky' experiments, many of which layed the foundations for successful programmes such as our current *Burkholderia* antibiotic discovery research.

FotografiaBasica/iStock

Antimicrobial resistance, antimicrobial peptides and drug repurposing

Thomas Vorup-Jensen, Stig Hill Christiansen and J. Eskild Petersen

Antimicrobial resistance (AMR) defines the ability of a microbe to resist a medicine, which once could be effectively used for its treatment. This situation is emerging as a major problem in healthcare globally. A closer look at the recent literature, in particular with a clinical microbiology perspective in mind, quickly points to AMR as multifaceted in origins, and hence, not a single problem. This has consequences for how to approach the treatment of infections and especially how and when to focus on new drug therapies.

AMR is associated with both healthcare and community-produced factors. One problem is the poorly regulated and poorly enforced use of antibiotics in agriculture and human healthcare in many low- or middle-income countries causing bacteria to become resistant. One would suspect overuse as key to AMR, but lack of compliance with recommended dosages and duration of therapy are also components as shown for instance in multi-drug-resistant tuberculosis (*Mycobacterium tuberculosis*). Another community-produced factor is the contact between humans and animals. Recent studies in Africa show how differences in the interaction with husbandry strongly influence microbial resistance patterns in human populations, even when antimicrobial medication is not a part of the equation. Community-produced AMR factors are certainly key to the future use of antibiotics, as they are by far quantitatively dominating.

The effectiveness of antibiotics

The induction of AMR in patients receiving regular treatment with broad-spectrum antibiotics is exemplified in cystic fibrosis (CF). CF is a rare, inherited disease, which affects the epithelium lining in several organs, including the respiratory system. CF patients suffer repeated lung infections, especially with *Pseudomonas* and *Burkholderia* species. According to data from the UK Cystic Fibrosis Survey, the median expectation of life for a CF patient for the years 2000–2003 averaged around

40 years, and projections suggest a rise to 50 years for the birth cohort of the year 2000. This owes much to better and more therapy options. Even so, the effectiveness of important antibiotics, such as the carbapenems and aminoglycosides, is reduced by AMR in Gram-negative bacteria.

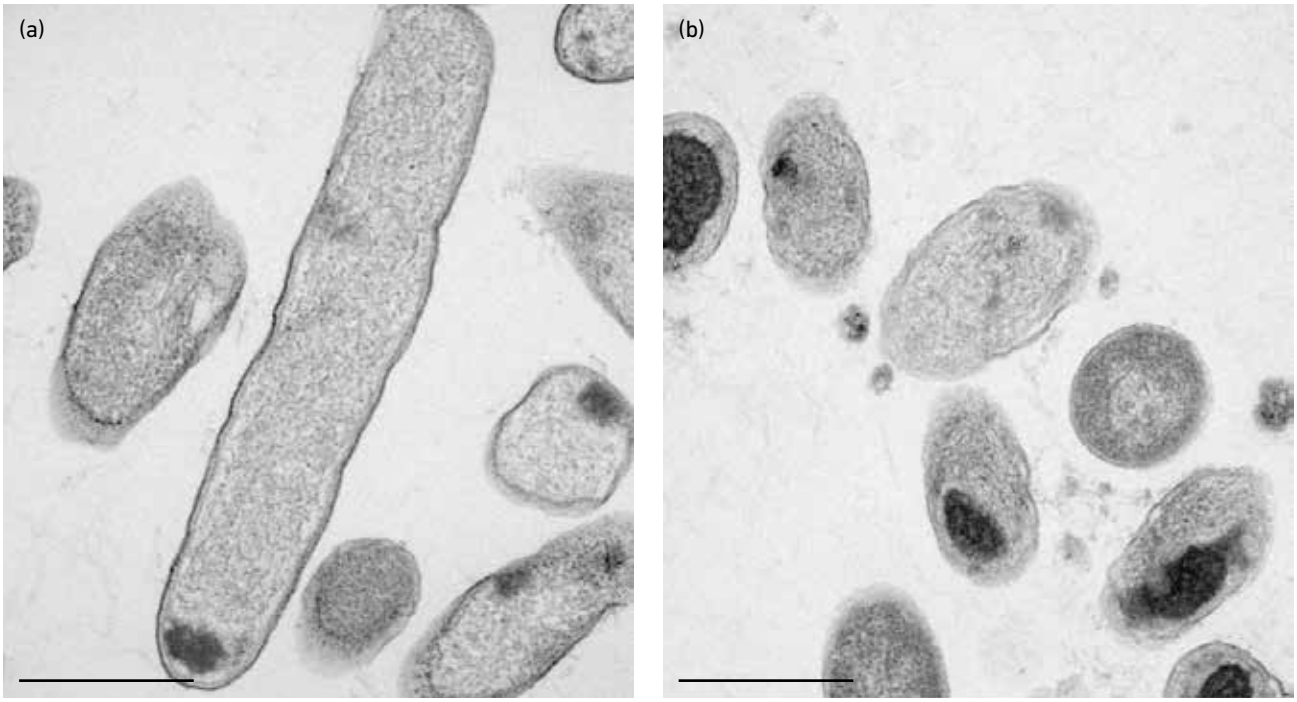
In recent years, the polymyxins, most particularly colistin, have made a comeback, still showing *in vitro* activity against carbapenems and aminoglycoside-resistant Gram-negative bacteria. Polymyxins belong to the class of polypeptide antibiotics and essentially work by breaking up the bacterial cell membrane. Colistin, or polymyxin E, was originally introduced for human use in 1959, but was largely shelved in the 1980s due to toxicity issues, primarily kidney failure. The re-introduction to treat AMR has been particularly useful in CF lung infections where the drug can be inhaled, limiting systemic side effects. This makes CF patients an obvious target group for new antibiotics that can be inhaled.

New drugs against the Gram-positive meticillin-resistant *Staphylococcus aureus* (MRSA), including linezolid, clindamycin, daptomycin and telavancin, have been brought to the market over the past decades. The latest introduction of new antibiotics also effective against Gram-negatives was the quinolones at the beginning of the 1980s and the carbapenems at the end of the 1980s. The newest development is the combination of carbapenems, including cephalosporins, with carbapenemase inhibitors (for instance ceftazidime/avibactam), which is now licensed in many countries. However, introduction of new antibiotics in human infectious diseases will not solve the AMR problem unless it is followed up by enforcement of restrictions for veterinary use, rigorous antibiotics stewardship and hospital infection control – a One Health approach.

New applications for existing medicines

Drug repurposing is the process of using a known drug for new indications. Unlike simple 'off-label' use, drug repurposing involves a systematic evaluation of the safety profile of drug candidates and also often a new formulation of the pharmacological active ingredient. The recorded application of an older drug provides knowledge of the pharmacodynamics, which make it possible to spare elaborate safety trials for new applications. Thereby, development costs are lowered compared to more standard drug development. Drug repurposing can involve large-scale screening programmes, but such an approach makes the availability of vast drug libraries a requirement.

Recently, we published a study demonstrating that the multiple sclerosis (MS) drug glatiramer acetate (GA, or Copaxone™) also has an anti-bacterial effect, especially against Gram-negative bacteria. It is beyond the scope of the present account to bring forward the complex origins of this drug; however, in the late 1990s, GA was a landslide in the treatment of MS. GA is a composition of random peptidic co-polymers, each on average 50 residues long and with residues of glutamate, lysine, alanine or tyrosine. In principle, this permits the formation of more than 10^{30} different co-polymers. The amino acid composition was regulated to mimic biochemical properties of myelin basic protein, a membrane-associated protein in the lipid sheath of neural axons and presumably one of the autoantigens in MS. As suggested by the name, myelin basic protein carries a high positive charge, which, in turn, is also a hallmark of GA, but also a known property of many antimicrobial peptides (AMPs). With an additional hydrophobic character, leading to self-oligomerization, GA resembles the biochemistry of AMPs. With these observations as basis for our hypothesis, we tested the antimicrobial activity towards *Pseudomonas* of the plain GA formulation. Much to our surprise, GA surpassed the activity of the human cathelicidin-fragment LL-37 in 100% human plasma. The extraordinary heterogeneity of GA has been one of the conundrums in understanding its pharmacological mode of action in MS. But as an antimicrobial formulation, there is a relevant comparison among naturally occurring AMPs, namely the group of temporins secreted in the mucus of the European red frog, *Rana temporaria*. Direct investigations showed that temporins together created synergy. With ten forms originally identified in *Rana*, the heterogeneity of the temporins is far less than for the GA co-polymers, but this natural defence mechanism encourages the speculation that the antimicrobial activity of GA originates



Electron microscopy micrograph of *Pseudomonas aeruginosa* as (a) untreated and (b) treated with GA. Note the formation of intracellular aggregates, which may be part of the antimicrobial effects. Bars, 500 nm. Stig Hill Christiansen

through similar mechanisms as for the synergetic temporins.

Our work to provide antimicrobial CF inhalation therapy brings into focus which part of the AMR problem is solvable by the application of new antibiotics. We reported that clinically isolated *Pseudomonas* strains with multi-resistance to classic antibiotics were killed by GA. In terms of the significance of new antibiotics development and AMR, we find it necessary to point out that CF-related AMR and community-produced AMR are different challenges when the social setting is included. Community-produced AMR is often caused by ill-informed overuse or *ad hoc* interactions with husbandry and its products. Directly opposite, AMR in CF emerges from a well-defined clinical need to use intensive antibiotic therapy in critical care facilities. This implies that new antibiotics are hardly a solution to the AMR problem in its widest sense, while the treatment of the relatively small group of CF patients infected with AMR bacteria has some hope in the benefits from the availability of more antibiotics.

To our knowledge, the current use or developments of AMPs as antimicrobials is limited to topical applications including inhalation. There is little doubt from numerous scientific studies that AMPs hold a broader promise. If the clinical application of AMPs is hindered by developing costs, drug repurposing could be a way forward, as we have tried to highlight here. The surprising finding of the antimicrobial activity of GA seems to suggest a way forward with hypothesis-driven investigations of older drugs. This should inspire more investigations along the route of drug repurposing.

Further reading

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Thomas Vorup-Jensen

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Thomas Vorup-Jensen, PhD DMSc, is Professor of Biophysical Immunology with a focus on the pharmacological-mode-of-action of protein-based anti-inflammatory drugs. He has also contributed to the scientific understanding of the innate immune system, notably the complement system, with a focus on the biochemistry of integrin complement receptors.

Stig Hill Christiansen

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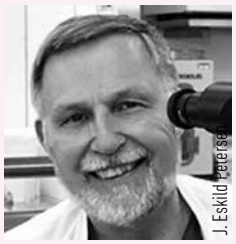
Stig Hill Christiansen, PhD, currently holds a postdoctoral fellowship at the University of Southern Denmark. Dr Christiansen has a particular interest in innate immunology, but as science has indeed become more multidisciplinary, his interests today range from immunology, through protein chemistry, to microbiology.



J. Eskild Petersen

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Dept. of Clinical Medicine, Aarhus University, Aarhus, Denmark;
Dept. of Infectious Diseases, The Royal Hospital, Muscat, Sultanate of Oman

J. Eskild Petersen, MD DSc, is Professor of Tropical Medicine. His scientific work has focused on toxoplasmosis and malaria. As a clinical specialist and consultant in infectious diseases, he has worked in Europe, Africa and the Middle East. He has also focused on treatment of infections in adult cystic fibrosis patients.

What parts of your job do you find most challenging?

Thomas: I very much like working in an interdisciplinary environment, where several scientific disciplines work together to solve questions in immunology or medical microbiology. To run a project involving several very different professional backgrounds is challenging, especially when findings made by one group of people needs explanation by another group. Likewise, when a paper is written up, merging the scientific vocabulary of several disciplines into one coherent text is part of this challenge.

Stig: The most challenging part of my job is the occasional need to change perspective when working with scientific problems.

Eskild: It is a challenge but also very rewarding to work with specialists with different backgrounds and assemble a team focused on a research issue. In the complex research environment of today, where everyone is very sub-specialised this is where new results and insights are generated.

What inspired you to become a microbiologist?

Thomas: I am an immunologist trying to relate the structure of proteins to their function in the immune system. Some of our work touches upon how the architecture of microbial surfaces has impacted the structure of proteins, and how our bodies use this as a defence against microbes. It is an awe-inspiring revelation to discover the structural logic of these molecular mechanisms.

Stig: In fact, I do not consider myself a microbiologist, but more an immunologist. My research spans a broad range of topics, focusing largely on innate immunology, but since my first microbiology lesson, I have been fascinated by infectious diseases and the micro-organisms that cause them. I am particularly interested in antimicrobial peptides and how bacteria use various resistance strategies to avoid antimicrobial peptide killing.

Eskild: Microbiology is a key specialty between clinical science and basic cellular science. The molecular revolution over the past thirty years has given us great insight into the functions of bacteria and not least the complicated mechanisms involved in antibiotic resistance. This can have direct clinical implications for the treatment of patients and the epidemiology of resistant micro-organisms.

Annual Conference **2020** #Microbio20

Monday 30 March–Friday 3 April 2020
Edinburgh International Conference Centre (EICC), UK

The Microbiology Society will celebrate its 75th anniversary in 2020. To celebrate this milestone, the organisation's flagship Annual Conference will – for one time only – be extended to five days and will take place in Edinburgh between Monday 30 March and Friday 3 April 2020.

This prestigious meeting will be held at Edinburgh International Conference Centre (EICC) and will include an additional first day (Monday) dedicated to the theme of Alexander Fleming and including a series of high-profile Fleming Lectures.

This will be followed by the standard four days (Tuesday, Wednesday, Thursday and Friday) of scientific sessions. As ever, these sessions are designed to demonstrate the impact and potential of microbiology to address important global challenges.

EICC

Monday 30 March 2020
Edinburgh International Conference Centre (EICC), UK

On the first day of Annual Conference 2020, the Microbiology Society will be hosting a special day-long series of Fleming Lectures organised by an appointed committee of previous Fleming Prize winners, chaired by Nobel Prize winner Sir Paul Nurse.

Compèred by Alice Roberts (University of Birmingham, UK) and with a keynote from Bonnie Bassler (Princeton University, USA), the day will offer an opportunity to hear the legacy of some of the past Fleming Prize winners and will focus on the influence of both established and up-and-coming scientists in addressing global challenges.

The day will feature presentations from a global speaker line-up, including:

- **Luke Alphey**, Pirbright Institute, UK – Genetic control of mosquitoes
- **Liz Sockett**, University of Nottingham, UK – Predatory *Bdellovibrio* bacteria – 58 years of understanding them as allies against AMR infections
- **Grant Jensen**, CalTech, USA – Visualizing bacterial nanomachines *in situ* by electron cryotomography
- **Eddie Holmes**, University of Sydney, Australia – The expanding virosphere
- **Mark Pallen**, Quadram Institute, UK – Palaeomicrobiology: what ancient DNA can tell us about pathogens from the past
- **Stirling Churchman**, Harvard University, USA – Orchestrating gene regulation across the genome and across the cell

Early career microbiologists can attend the Fleming Showcase day for free when registering for Annual Conference 2020. Further information about the day can be found on our website (**microbiologysociety.org/microbio20**).

Keep up-to-date with events on Twitter: **@MicrobioSoc**

rabbit75_ist/Thinkstock

Destination Edinburgh

Edinburgh is a diverse and vibrant city, steeped in history. The backdrop of Arthur's Seat, the Pentland Hills and Edinburgh's waterfront make the city an exciting event destination. If you extend your stay after Conference, there are plenty of attractions to visit, such as Edinburgh Castle, the National Museum of Scotland, the Scottish Parliament and the Royal Yacht Britannia. Visit 'This is Edinburgh' (**edinburgh.org**) for further information.

Registration

Registration is now open for Annual Conference, which attracts over 1,600 attendees for the UK's largest annual gathering of microbiologists.

To ensure the meeting remains of value for this broad microbiology community, ticket prices have not increased from last year beyond the rate of inflation. A 10% discount is available for anyone registering for all four days of the meeting and registered early career microbiologists can attend the Fleming Showcase for free.

Further information can be found on the event page of the website (**microbiologysociety.org/microbio20**).

Abstracts

Abstract submission is now open and submission information is on the website.

As always, Annual Conference is designed to cover the breadth of microbiology research, so don't miss out on this opportunity to showcase your microbiological work and research to this broad scientific community. Submissions close on **9 December 2019**.

Notifications of acceptances will be made **from 14 January 2020**.

For those abstracts that are awarded a poster presentation, Annual Conference provides an excellent platform for emerging scientific research. Posters will be rotated to ensure relevance to the content of the day's live programmed sessions. See the website (**microbiologysociety.org/microbio20**) for further information and submission categories.

Early career microbiologists

Annual Conference has many opportunities for early career microbiologist members to get involved. If you're eligible, don't forget to indicate your interest in participating in the Sir Howard Dalton Young Microbiologist of the Year Competition, and/or the Early Career Microbiologists' Forum Co-chairing scheme.

Conference programme

Annual Conference 2020 has over 30 scientific sessions, covering topics across the breadth of microbiology, and workshops, forums and symposia specifically aimed to help with professional development and cross-disciplinary learning. You can view the current 2020 programme online, including a list of the invited speakers and their talk titles and abstracts.

Social programme

Annual Conference is designed to offer ample opportunities for formal and informal networking for both early career and established microbiologists. Two low-cost, separately bookable events are taking place as part of the social programme in 2020.

On the Tuesday evening (31 March 2020) of Annual Conference week , VisitScotland's five-star-rated attraction **The Real Mary King's Close** will be opened up exclusively for registered Society delegates. On Thursday evening (2 April 2020), the ever-popular **Annual Conference Quiz** will be taking place at Ghillie Dhu – a dramatically vaulted Georgian converted church in the shadow of Edinburgh castle.

Prices, times and further details about all socials can be found on the event website.

Grants

Society Conference Grants are available to support eligible members wishing to present at the Annual Conference. The grants deadline is **20 January 2020**. Grant notifications will go out before **31 January 2020**. Full information is available on the Society Conference Grant page (**microbiologysociety.org/societyconferencegrants**). If you are a member who is not eligible for a Society Conference Grant, please apply via the Travel Grant scheme: (**microbiologysociety.org/travelgrants**).

Accommodation and travel

If you're planning on joining us at this important event, we highly recommend you secure your accommodation and make your travel plans as early as possible. Edinburgh is a popular destination city and hotels fill up quickly.

To support you in securing your accommodation, you can book through our booking and accommodation services agent Reservation Highway (**reservation-highway.co.uk/micro20**). The agency has secured a range of accommodation options to suit all budgets throughout Edinburgh, at discounted rates.

To get the latest Annual Conference news and updates, follow us on Twitter **@MicrobioSoc** using the hashtag **#Microbio20.**

Focused Meetings 2019

The conferences and events team delivered five successful Focused Meetings throughout the year, rounding off the 2019 programme. The Focused Meetings are key events in the Society's calendar, presenting opportunities for microbiologists with shared interests to explore new scientific research, form new connections and hear from a varied line-up of distinguished invited speakers.

Anaerobe 2019: Changing perceptions of anaerobic bacteria; from pathogen to the normal microbiota and back

13–14 June 2019 | Jurys Inn Cardiff, UK

Our first Focused Meeting of the year took place in Cardiff and was organised in collaboration with the Society for Anaerobic Microbiology and Welsh Microbiological Association.

The meeting was very well received, as it provided scientific insights into the future impact of anaerobic bacteria in human health and disease, addressing the implications of recent microbiota studies as well as the continued threat of emerging and re-emerging anaerobic infection.

British Yeast Group 2019: Discovery to Impact

26–28 June 2019 | County Hotel, Newcastle, UK

The Microbiology Society was pleased to once again incorporate the 'BYG' meeting into its Focused Meeting programme this year, bringing together members of the British Yeast Community at this long-standing annual event.

Over 70 delegates from throughout the UK and beyond enjoyed three days of fantastic science, exploring the theme of Discovery to Impact. The meeting also featured a varied social programme, offering delegates plenty of opportunities to make new connections, discuss research projects and strengthen relationships in the scientific community.

IMAV 2019: International Meeting on Arboviruses and their Vectors

5–6 September 2019 | University of Glasgow, UK

The third IMAV: International Meeting on Arboviruses and their Vectors took place in Glasgow in September and proved again to be a great success.

This series of meetings is getting stronger and stronger and becoming a must-attend event for the arbovirus research community. We look forward to the next meeting in 2021.

Microbes in Medicine: A Century of Microbiology at Trinity College Dublin

24–25 October 2019 | Trinity College Dublin, Ireland

In 2019 the discipline of microbiology celebrated its centenary year and we marked the occasion at the penultimate Focused Meeting of our 2019 programme.

The meeting, at Trinity College Dublin, brought together scientists and medical practitioners with an interest in the use of microbes and microbial products to treat and prevent diseases to hear a range of fascinating talks from renowned invited speakers and early career researchers. The Society was pleased to incorporate a special presentation from session organiser, Charles Dorman, who delivered the prestigious Trinity College Dublin Inaugural Lecture to meeting delegates and a range of invited guests.

Antimicrobial drug discovery from traditional and historical medicine

29 October 2019 | Ashmolean Museum, Oxford, UK

Great networking opportunities were created at the Focused Meeting: Antimicrobial drug discovery from traditional and historical medicine in Oxford. This new format meeting has been very positively welcomed by attendees and helped to build new effective networks for researches from a range of fields including microbiology, chemistry, botany and the history of medicine.

Focused Meetings 2020

Our 2020 Focused Meeting programme is now online – visit our website (**microbiologysociety.org/events**) for the most up-to-date information. Don't forget that our Scientific Conferences Committee is always open to new proposals to become part of our future events programme.

Why not discuss your ideas with our Head of Conferences and Events, Laura Crick (**l.crick@microbiologysociety.org**)?

Candida and Candidiasis 2020 – Abstracts open

Abstract submission is now open for Candida and Candidiasis 2020, taking place in Montreal, Canada, 19–23 April 2020. The abstract deadline is 9 January 2020.

Further details can be found at **microbiologysociety.org/candida2020**.

Call for Annual Conference Sessions Proposals

The deadline to send your session ideas for our Annual Conference 2021 is **16 December 2019.** We welcome session suggestions from members working in any field of microbiology. If you have an idea for a session and would like it to be considered by our Divisions at our next conferences and events planning day, we want to hear from you. The Divisions meet in January every year and if your suggestion is accepted, the Scientific Conferences Committee (SCC) will appoint experienced session organisers to finalise the session programme. Visit our website (**microbiologysociety.org/events**) to download the suggestion form.

Society-Supported Conference Grants

The Microbiology Society provides financial support for events held by members in all areas of microbiology. The deadline for the next round of applications for a Society-Supported Conference Grant is **16 December 2019**. Members can apply for a grant of up to £2,000 towards covering the costs of invited speakers, travel and accommodation. More information, including the eligibility criteria and the application form, can be found on our website at (**microbiologysociety.org/ssconferencegrants**).

Members at the networking event.

Annual General Meeting and Showcase of the Society's Achievements

Each year the Society hosts a showcase event, before our Annual General Meeting, for early career members of the Society to come together, meet each other and learn from other members of the Society who are further on in their careers.

The event allows us to recognise the excellent work our Committee members, Champions and Prize Winners have accomplished over the past year.

This year's event, which took place on 12 September 2019, at The Law Society, London, began with a talk from Dr Lindsay Hall on 'Building and being a part of a team', followed by a series of networking activities for our early career members which focused on bringing together ideas and how to work collaboratively as a team.

Guests were then invited to view posters from the Annual Conference poster prize winners during lunch, before the final of the Sir Howard Dalton Young Microbiologist of the Year (YMOY) Competition began. The nine finalists were shortlisted from a range of oral and poster presentations given at the 2019 Annual Conference, 2018 Irish meeting and 2018 Annual Conference.

Each finalist gave a fantastic presentation of their research in another hard-fought competition. The Society congratulates all of the finalists and thanks those who took part in the competition. The winner was then announced at the evening reception. Congratulations to Davis Laundon, from the Marine Biological Association, University of East Anglia, for winning first prize for his talk 'Shining new lights on chytrid cell biology: quantitative live cell imaging of rhizoid development in an early-diverging fungus', and to second and third-prize winners Sarah Worsley and Michaela Conley, respectively.

Davis Laundon and President Professor Judith Armitage.

Matt Hutchings.

Davis said of winning the prize: "The competition was absolutely amazing this year. I thought every presentation was excellent and incredibly well communicated. To be awarded the prize amongst those presentations was a really huge honour and incredibly flattering."

After the business of the AGM, the final celebration of the day was Professor Matt Hutching's Microbiology Outreach Prize talk on his outreach project 'Antibiotic Hunters'.

Matt explained that the project is about "our hunt for antibiotics ... and the kind of weird and wonderful places that we try and find them".

Watch Q&As with both Davis Laundon and Matt Hutchings on our YouTube channel (**microbiologysociety.org/youtube**).

Spotlight on grants: Education and Outreach

Education and Outreach Grants support a variety of science teaching and engagement activities, providing members with opportunities to improve microbiology teaching, outreach and communication to many different audiences.

Earlier this year, PhD student Sabastine Arthur (University of Cambridge, UK) was awarded a grant to support his outreach project, 'Be aware of Infectious Disease Epidemic' (BIDE), in Ghana. The aim of this project was to demonstrate to school children how an infectious disease outbreak can be diagnosed and managed within a community. The method of engagement was adopted from Dr Lucy Thorne (University College London, UK) and Professor Ian Goodfellow (University of Cambridge, UK) with whom Sabastine worked with closely over the course of the project. Sabastine also worked closely with Ghana-based NGO 'Vacation Initiatives in Science, Africa' (VISA) and 'Hardie Wren Development Initiatives' to organise the project from Ghana and the UK, respectively.

Post-engagement activity photo of a group of volunteers and school children of Labone S.D.A Basic School, Accra, Ghana. VISA

Sabastine said the project provided "an opportunity to discuss the importance of vaccination and encouragement of personal hygiene in preventing disease outbreak."

The programme ran for four days and over 200 school students participated. Students were given a short series of lectures and practical sessions to inform them about common infectious diseases, such as Ebola and measles, and how we can identify them. They also learned how an outbreak may arise and subsequently how infection can spread beyond their schools – through homes, hospitals and wider communities.

Students could then apply what they had learnt to a series of incidence outbreak case studies. This involved performing glucose tests on simulated blood samples and analysing Lego-brick-built sequences of DNA that corresponded to a host of pathogens.

To end the programme, a local journalist was invited to engage students through a series of question and answer sessions. This enabled them to reflect on what they had learnt and effectively communicate this to a wider audience.

School children aided by volunteers to perform experiments to identify an infectious disease agent in an outbreak incidence. VISA

Sabastine said the highlight of his project was that it enabled his team to "deconstruct the myth that science is a difficult discipline to pursue, and that anyone can do science irrespective of their gender, financial background or social status."

Since returning from Ghana, the project has developed so that it can be run by Sabastine's group of volunteers in different institutions and regions across Ghana. The team are now planning to set up a lab that will be involved in engaging children in several practical science activities in line with the Ghana Education Service science curriculum.

Applications for the Education and Outreach Grants open twice a year, in January and June, with deadlines in April and October, respectively. To find out more, visit our website (**microbiologysociety.org/educationandoutreachgrants**).

To find out more about the wide range of grants available to support Microbiology Society members, visit the grants area of our website (**microbiologysociety.org/grants**).

The new face of *Microbiology*

***Microbiology* is the Microbiology Society's founding and flagship journal. The journal publishes fundamental and applied research across the breadth of the field of microbiology and supports the exchange of knowledge on key topics such as new and emerging diseases, antimicrobial resistance, food security, environmental sustainability and health.**

We spoke to Tanya Parish, Editor-in-Chief of *Microbiology*, and Gavin Thomas, Deputy Editor-in-Chief, to outline why *Microbiology* remains an important place to publish and how its revised scope will better meet the needs of the microbiology community.

Why is *Microbiology* important, and why are you involved with it?

Tanya Parish (TP): *Microbiology* is the flagship journal of the Society, playing a pivotal role in the dissemination of information between microbiologists. It aims to connect scientific communities and stimulate ideas and new research. I have been associated with the journal for many years, as an Editor, then Senior Editor, and finally Editor-in-Chief. As a scientist, it is important to me to include activities that benefit other microbiologists – whether that is reviewing papers, discussing methods and approaches with students at meetings, or in this case, taking on the responsibility of developing new initiatives with the journal. In addition, I felt it was an important way to ensure that we address issues of gender representation and diversity. And, of course, I got to continue working with some fantastic colleagues, both on the Editorial Board and in the Society's Publishing Team.

Gavin Thomas (GT): As a member of the Society for almost 20 years now, I have benefited massively from its activities in my career, and so have my PhD and postdoctoral students. From my first meeting, I was welcomed into the family of microbiologists and found the Annual Conference as the main way to learn about the best new science and meet the scientists themselves. I got a travel grant to enable me to attend this first meeting; membership for students was cheap and they sent me a magazine with lots of cool articles and news. As I became a Principal Investigator myself and grew my own group, I was delighted to become an Editor for the journal and then later Senior Editor, and it became clear to me how important the journal is for running all the other activities of the Society. The continued success of *Microbiology* is central to the continued success of the Society. By working with our membership who benefit most from the success of *Microbiology*, we need to revitalise the journal to make it an exciting place to publish. 'Publishing for the community' is our tagline and this is really true – it's about the microbiology and ensuring the future of the Society.

Why have you changed the scope?

TP: Microbiology has been important since the beginning of civilisation, from many perspectives. *Microbiology* has always aimed to cover the widest breadth of research, reflecting its key role in science and society. As new research areas develop and old areas change, we need to keep up with these developments. Our scope sets out the journal's scientific vision and provides a home for all those new areas. For example, microbiology will play a key role in delivering the United Nations Sustainable Development Goals. We have broadened our scope to include newer areas like microbiomes and antimicrobial development, as well as applied and translational research, but have also tried to simplify the way we present it, so it is more welcoming. We are looking for articles that advance our knowledge in the broadest sense. Articles should include novel work, be conducted to rigorous methodological and ethical standards, and have sound conclusions.

Why should members publish with *Microbiology*?

TP: We have a robust and fair peer review process, overseen by a world-class Editorial Board; a fast time-to-publication for accepted papers; it's free to publish and we have a liberal Open Access policy. For Society members, most importantly, we provide financial support to other Society activities.

GT: We are making the link between the journal and the Society much clearer to members. We are also starting new activities to promote the link of the journal to the community, the first of which is the creation of the **actinobase.org** wiki.

TP: Members can also get involved by volunteering for the reviewer database or putting their name forward to be considered as an Editor. Suggestions for collections, special issues and/or Focused Meetings are also welcomed.

Where do you see the journal in five years?

TP: Microbiology as a field is always developing, so we may see new areas being included. The biggest changes we expect to see are not in terms of publications, but in the work we do, in the broader sense of supporting communities. Over the past five years, we have introduced two new article types, graphical abstracts, a board of reviewers and a volunteer reviewer database, as well as poster and speaker prizes at conferences, and we expect to continue introducing new initiatives.

GT: I want to see scientists fully engaged with the journal again and publishing their work there as a matter of choice. When you have a solid piece of work you want to be well reviewed and well read then you should publish in a Society journal to help support our work, rather than the shareholders of commercial publishers.

Reviving the antibiotic research and development pipeline: marine natural products

The growing threat of antimicrobial resistance (AMR) has brought into sharp focus the pressing need for the development of new antibiotics. Already, AMR is estimated to cause at least 700,000 deaths around the world each year.

That figure is predicted to rise to 10 million, alongside a cumulative cost of $100 trillion, by 2050 if no action is taken. The barriers to bringing new antibiotics to market hinge primarily on the lack of return on investment. Unlike drugs that treat the symptoms of chronic disease, antibiotics offer a relatively poor return on investment because they are taken for a short period of time and cure their target disease. Moreover, prescribing a new antibiotic is likely to be restricted for fear it will become resistant. The many market failures and the high cost of AMR are not currently reflected in the cost of the drugs. As a result, many large pharmaceutical firms have exited the antibiotic space in favour of more profitable therapeutic ventures. These moves are seeing smaller biotech companies occupying the space and developing new antibiotics, as well as increasing pressure on public-led funding to support the development of new products.

In response to this growing crisis, numerous major international and national initiatives aimed at financially incentivising antibiotics research and development (R&D) have been implemented. Support for R&D can be split into two broad categories of incentives: push and pull mechanisms. Push mechanisms share R&D costs across several parties to reduce a firm's outlays and to increase the net present value (NPV) of their antibiotic candidates. They include research grants, tax incentives and public–private partnerships. Instead of sharing costs, pull mechanisms increase NPV by guaranteeing or increasing the revenue of a new antibiotic. This can be through policies that accelerate the regulatory pathway, extend market exclusivity or provide a direct monetary contribution. The UK 5-year action plan for antimicrobial resistance (2019–2024) sets out a new payment model that will reimburse pharmaceutical companies based on how valuable their drugs are to the National Health Service (NHS), rather than on the quantity of antibiotics sold. This UK pilot project will be the world's first delinked pull incentive for

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antibiotics. The upfront payment with the new model is expected to encourage drug makers to invest the estimated £1 billion required to develop a new medication, as they can be reassured that they will still be paid for the drug even though it may be stored for reserves. Rebooting the antibiotic R&D pipeline requires global support. For this reason, the UK initiative will be evaluated from the start and findings will be shared with the rest of the world so that other healthcare systems can test similar models.

Searching for antibiotics in the abyss

At the University of Bristol, Dr Paul Race and colleagues are combining the innovations of synthetic biology with robotic environmental sampling to attempt to unblock the antibiotic discovery pipeline. The 'antibiotics in the abyss' discovery team ventures deep into the ocean, one of the most extreme environments on Earth, to find micro-organisms that have been exposed to evolutionary pressures that necessitate the acquisition of unusual metabolic innovations and are therefore considered to be excellent sources of novel natural products. Marine natural products could contribute to reviving the antibiotic discovery pipeline, as they are an untapped reserve of potential antibacterial agents. After running the project for only 18 months, the Bristol team had already isolated more than 1,000 previously uncharacterised micro-organisms, and six new natural product-based antibiotic leads. However, Dr Race explains that the lack of funding mechanisms bringing academia and industry together is a blocker in realising the potential of what might already be available. He also points to the O'Neill Report ('The Review on Antimicrobial Resistance' commissioned in 2014 by the UK Prime Minister, who asked economist Jim O'Neill to propose concrete actions to tackle the global problem of AMR) and its numerous suggested solutions to circumvent economic barriers and expedite antibiotic discovery: "the crux of the problem is that there is a plan but nobody to pick up the baton and make that plan a reality", says Dr Race. He also highlights the need to keep pressing for more investments in all aspects of AMR research, underlining that, "big problems require big money" and to develop a global initiative that would bring together those working across the pipeline of drug discovery and clinical development: "it is only by working in an integrated manner and with a significant amount of dedicated resources that we can win the global fight against AMR".

Find out more about Dr Paul Race and the 'antibiotics in the abyss' team on their website: **microb.io/2AD1TeM**.

The Microbiology Society published a news story about the UK 5-year AMR strategy and 20-year vision, available on our website: **microb.io/2DFC6oB**.

Please visit the 'A Sustainable Future' page on the website for further details on how AMR represents a global threat to health and well-being, as well as opportunities to contribute to the project: **microbiologysociety.org/SDGs**.

Reflections on being a member of the Microbiology Society

When we ask members why they joined the Society, we get a diverse range of responses. We have members in over 90 countries, ranging from those still studying, through to those who have completed successful careers in academia, research, industry and public service. As we approach our 75th anniversary year, we thought you might be interested to hear about members' experiences of being part of our global community.

My first (unsuccessful!) job application in 1982 was to the Society, to join the *Journal of General Microbiology* (now *Microbiology*) team. I became a member in 1983 on the advice of my PhD supervisor, Dr Tony Roberts.

I have been a member of multiple societies, but the Microbiology Society has always felt like my professional home. Conferences have been important for maintaining a wide microbiological perspective, but I also gained vital early-career committee and conference organisation experience. A grant from the Society enabled me to work in the Hancock Lab (University of British Columbia, Canada). So, membership has provided me with important development opportunities and enabled me to work and form friendships with many members of the international microbiology community.

Deirdre Devine
School of Dentistry, University of Leeds, UK

I've been a member since 1986, having trained in the UK, but I have spent most of my working life in the US. As a result, I haven't been able to participate in as many conferences and events as I may have liked to. However, I very much believe in your mission and want to give something back to UK microbiology through the Society. Being a member has enabled me to do that.

David Leib
Geisel School of Medicine, Dartmouth College, USA

In 1989, as an Australian, medically-qualified student undertaking his PhD in Cambridge, I joined the Society for General Microbiology (as it was then), as did many of my fellow students and postdocs. For me it was a way to integrate into a group of like-minded researchers and see, first-hand, the excellence that was, and is, British science and critical thinking.

The Microbiology Society provided an initial welcome that was unconditional, and since then it has been a great journey. The formal meetings, and informal opportunities to hear, and speak, with senior virology researchers who had great depth and understanding, meant I saw my work in the context of much longer and more complex scientific endeavours. That sense of belonging, intelligent discourse and engagement meant a lot early on in my career, and continues to this day, despite time and distance.

William Rawlinson
The Prince of Wales Hospital, Australia

When I was in the Sixth Form at school there was very little mention of anything to do with microbiology. The emphasis was on a thorough grounding in physics, chemistry and mathematics, and any plant or animal that could be readily seen without the use of a microscope! My degree course in Biological Chemistry alerted me to the new world of fungi, but bacteriology was only taught to medical students, apart from a few lectures on legume nitrogen-fixing bacteria.

All was to change when I was awarded a Civil Service Commission Post Doctorate Fellowship on the development of improved vaccines against bubonic and pneumonic plague at the Microbiological Research Establishment, Porton Down. I just *had* to learn more about microbiology! Joining the Microbiology Society in 1958 enabled me to learn about the latest advances in mycology and bacteriology from the world's leading microbiologists, including Professor Harry Smith FRS.

The integration of microbiology teaching into degree courses in botany was made so much easier by the expert guidance of researchers, many of whom were members of the Microbiology Society. Many today are still as willing as ever to lend a helping hand.

Edward Cocking

Emeritus Professor, University of Nottingham, UK

I came to the Microbiology Society in 2014 as a second year PhD student when I attended the Annual Conference for the first time. The talks were amazing; I remember being hard pressed to choose which ones to listen to and where to go as there was so much going on. I was so mesmerised by the experience that I felt I had missed out by not joining in my first year! As a result, I became an active member and volunteered to become a Society Champion.

Membership has brought me so many opportunities and experiences. I'd say that I love the Annual Conference, *Microbiology Today* magazine, the outreach activities I have taken part in and the opportunities I've had to connect and network with so many other scientists. Having said that, the single most memorable opportunity for me was the chance to attend the Parliamentary Links Day, in which the future of science after Brexit was being discussed amongst the scientific community and government representatives. It was a real privilege to be part of this.

Marília Costa

Paraíba State University, Brazil

Joining the Microbiology Society in 2013 was one of the best decisions of my life. I was curious to learn more about microbiology and so I wrote and asked to join the Society. I was the first person to join the Society from Nepal! Soon, I joined the Champions programme and from the support of the Society I was able to organise a variety of events. The Society constantly encouraged me by featuring my work and events on the website and in *Microbiology Today* magazine. This also helped me get better recognised within my own workplace and among other organisations too. In 2019, I got a chance to attend the Annual Conference and experience the lectures, workshops and opportunities to meet other members and Champions. They could not have been more supportive. The Society is a great place to share ideas and work experiences and has really widened my understanding and perception of the field.

Manoj Pradhan

Nepalese Army Institute of Health Sciences, Nepal

Microbiology Society and MiSAC: 50 years of mutualism

Cutting the celebratory cake to mark the 100th MiSAC committee meeting, July 2008. Right to left: Janet Hurst (then Secretary) and current officers Margaret Whalley (Treasurer), John Tranter (Secretary), John Grainger (Chairman, centre) and John Schollar (Vice-Chairman, extreme left). MiSAC

In the 1960s the major professional biological societies became aware of an increased need in schools for support for the teaching of specialist aspects of biology in response to marked changes in curricula brought about by new developments such as Nuffield Biology. The response by the Microbiology Society (then named the Society for General Microbiology) was to organise a symposium from which arose a joint committee – the Microbiology in Schools Advisory Committee (MiSAC) – in 1969, consisting of representatives of the Microbiology Society and other organisations with experience of and interest in school education.

Following my appointment as the Microbiology Society representative on MiSAC in 1973, the associated activities between the two organisations began to flourish. I held the role as Microbiology Society representative until 1994, having become Chairman of MiSAC in 1983. Over this time, the activities of MiSAC were markedly reinforced by the appointment of Janet Hurst, a microbiologist with administration and writing experience, to the Microbiology Society staff. Janet became MiSAC Secretary in 1991, with support later from Dariel Burdass, a then new staff colleague who was also a microbiologist. The Microbiology Society also undertook administration of the MiSAC Annual Competition and provided space on the Society web server until MiSAC developed its own website.

Among the early contributions made by MiSAC was involvement in several revisions of the Microbiology Society schools booklet *Careers in Microbiology*. Encouraged by the growth in schools' activities, the Microbiology Society made funds available in 1983 for a Schoolteacher Fellow to produce practical activities, in a project directed by MiSAC to which Paul Wymer was appointed to work with me in the Department of Microbiology at Reading University. The major outcome of the project, the publication *Practical Microbiology and Biotechnology for Schools*, led the then Department of Trade and Industry to provide funds in 1985 to establish the National Centre for Biotechnology Education (NCBE) at Reading, where it still operates. With support from MiSAC and NCBE, the Microbiology Society also developed practical courses for teachers, technicians and postgraduate certificate of education (PGCE) students. These became a significant activity whereby John Schollar of NCBE and myself delivered some 100 such courses throughout England, Wales and Northern Ireland during the first decade of the 2000s. Other notable collaborations with MiSAC were the Microbiology Society publications *Practical Microbiology for Secondary Schools* (2002) and *Basic Practical Microbiology: A Manual* (2003).

In recent years, the Microbiology Society representative on MiSAC was drawn from Society staff, but is now again a role open to Society members, with the representative also being part of the Society Communications Committee. Rachel Exley was appointed to the position in 2018 and has quickly become very involved, including joining Margaret Whalley, MiSAC colleague and a member of the British Mycological Society, as co-editor of *MiSAC matters: 50th Anniversary Articles* (**misac.org.uk**). Several Microbiology Society members have contributed to this celebratory publication, including Sir Paul Nurse and President Professor Judith Armitage.

This year MiSAC celebrates its 50th anniversary. The close coincidence with Microbiology Society's 75th anniversary next year is well worth recording, because of both the key role that the Microbiology Society played in the formation of MiSAC in 1969, and the many ways in which a long-lasting and close association developed between the two organisations to support the future of microbiology.

MiSAC sponsors

British Mycological Society: **britmycolsoc.org.uk**
CLEAPSS: **cleapss.org.uk**
Microbiology Society: **microbiologysociety.org**
National Centre for Biotechnology Education: **www.ncbe.reading.ac.uk**
Quekett Microscopical Club: **quekett.org**
Scottish Schools Education Research Centre: **sserc.org.uk**

John Grainger
j.m.grainger@reading.ac.uk

Early Career Microbiologists' Forum Update: Looking forward: translating research and tackling mental health

I can't believe that this is my last *Microbiology Today* ECM Forum update! The Executive Committee was brand new when I joined, and it has been a privilege to see the Forum grow over these three years.

Your new Communications Representative will be Robert Will, a second year PhD student at the University of Cambridge, under the supervision of Gordon Dougan and Ankur Mutreja. He is investigating the global evolution and diversity of *Corynebacterium diphtheriae*. I spoke to Robert about the motivation behind running for the Executive Committee and his hopes for his term.

Congratulations on your election! Why did you decide to run for the Communications Representative position?

I was already a Microbiology Society Champion and was looking at ways to get more involved. When I saw that the Communications Representative position was open for nominations, I knew I had to go for it. I got the bug for science communication from my tutor at Swansea, Dr Dan Forman, who is one of those people that can make science interesting and fun to anyone! Discussing the role with you, Rebecca, and the current and former Chairs of the Forum made me really want to represent early career microbiologists.

What do you hope to achieve over your term?

The big thing I have found during my time as a student is how difficult it can be to decipher science without pre-existing knowledge. My main aim is to promote how amazing microbiology and the Society are, by looking at how we can increase opportunities for ECMs to get involved with microbiology communication.

My other aim is to work with my fellow ECM Forum Committee members to aid the Society in its efforts to support the mental health of ECMs. This is an important and well-documented issue for postgraduate students and we can build on the information already available at the Society.

Is there anything else you would like to add before I hand over the reins?

I wanted to say thank you to you Rebecca, for all that you have done over the past few years as Comms Rep! I would also like to mention the Microbiology Society Champions again; if you're interested, Paul Easton (**p.easton@microbiologysociety.org**), Head of Membership Services at the Society, can give you more information. Finally, thank you so much for all those who voted for me; I really appreciate it and I hope I live up to the trust you put in me!

Robert will officially begin his term in January, so if you have any questions or suggestions for him then please do get in touch. Good luck Robert!

Visit our website (**microbiologysociety.org/champions**) to find out more about the Society Champions scheme.

Rebecca Hall
Communications Representative, ECM Forum Executive Committee

Member Q&A

This is a regular column to introduce our members. In this issue, we're pleased to introduce Zina Alfahl.

Where are you currently based?

I am currently based in the United Kingdom and am studying for a PhD at the School of Pharmacy, Queen's University Belfast.

What is your area of specialism?

My research in microbiology focuses on the detection of pathogenic bacteria of potential clinical relevance in people with bronchiectasis.

And more specifically?

There are currently no guidelines for the management of bronchiectasis. My project focuses on the determination of the relationship between airway microbiome composition, inflammation and clinical outcomes in bronchiectasis, as well as informing the choice of both clinical and lab outcome measures for future clinical trials. This is likely to help with targeting new therapies in bronchiectasis.

Tell us about your education to date

I obtained my first-class honours Bachelor of Pharmacy degree from Al Ain University of Science and Technology, United Arab Emirates. I then moved to the UK to pursue my higher education at Queen's University Belfast with the Halo Research Group, which investigates infection in chronic lung disease, and the Northern Ireland Clinical Research Facility (NICRF) team under the supervision of Professor Michael Tunney and Professor Judy Bradley.

Where did your interest in microbiology come from?

My interest in microbiology started in the second year of my undergraduate degree, when I discovered that microbiology has a huge impact on our lives. I was keen to explore and find out more about microbes in the human body, and how microbiology helps us in curing many life-threatening diseases.

What are the professional challenges that present themselves, and how do you try to overcome them?

Working in a world-class laboratory was my dream when I started planning for my PhD, but at the same time I was aware that I had to commit a large amount of time and effort, which can be stressful. I learned how to handle stress and how to manage my time to achieve my targets. Moreover, the laboratory environment I am working in hasn't hesitated to help me to overcome any challenges.

What is the best part about 'doing science'?

The best part of 'doing science' is the ability to adopt and develop problem, solving strategies that can overcome any obstacles a scientist might encounter.

Who is your role model?

Any successful person in life I consider my role model. I am grateful for everyone in my life and there are many who inspire me.

Zina Alfahl

What do you do to relax?

I'm passionate about travelling. Travelling helps to relieve stress.

What one record and luxury item would you take to a desert island?

A scientific book and my mobile.

Tell us one thing that your work colleagues won't know about you.

I don't like complaining and wasting time.

If you weren't a scientist, what would you be?

A lawyer.

If you would like to be featured in this section or know someone who may, contact Paul Easton, Head of Membership Services, at **p.easton@microbiologysociety.org**.

Obituary

Professor Michael Rossmann 1930–2019

Professor Michael Rossmann, Hanley Distinguished Professor of Biological Sciences at Purdue University, USA, and recipient of the Microbiology Society Prize Medal in 2017.

In a career spanning over 60 years, Michael Rossmann made seminal contributions to the field of protein structure. Although possibly best known to microbiologists for his structures of icosahedral viruses, he was also the first to define conserved nucleotide-binding motifs in proteins (the *Rossmann fold*) and developed the molecular replacement method used to solve around 75% of structures submitted annually to the Protein Data Bank (PDB).

Michael was born in Frankfurt, Germany, and educated in the UK from 1939. His undergraduate degrees were in Mathematics and Physics from the University of London and his doctorate, in chemical crystallography, was from the University of Glasgow in 1956. After two years as a postdoc at the University of Minnesota, Michael moved back to the UK to join Max Perutz, John Kendrew and Dorothy Hodgkin in the Medical Research Council's 'hut' adjacent to the Cavendish Laboratory in Cambridge.

Michael worked with Perutz and Kendrew to solve the structure of haemoglobin, the first protein to have its structure reported. Following this, with David Blow, Michael developed novel phasing methods for solving protein structures. These methods, now known as molecular replacement, are fundamental to the solution of thousands of structures today.

In 1964, Michael moved to an Associate Professor position in Biological Sciences at Purdue University, Indiana. In 1978 he was appointed the Hanley Distinguished Professor of Biological Sciences at Purdue University, a position he held for the rest of his long career.

While at Cambridge, Michael learnt that the mathematical puzzles of crystallography, although challenging in their own right, provided the key to understanding nature, in particular the relationship between the structure and function of proteins.

At Purdue University, Michael conducted comparative structural analysis of divergent dehydrogenases and identified a fundamentally conserved protein fold that bound nicotinamide adenine dinucleotide (NAD). This *Rossmann fold* is the most common motif present in the PDB. More significantly, Michael proposed that proteins were composed of domains, each with a specific function and conserved structure. This concept is a fundamental principle of protein structure, function and evolution.

The methods Michael developed to interpret the non-crystallographic symmetry of dehydrogenses were then applied to rod-shaped plant viruses and icosahedrally symmetric viruses such as rhinovirus (the 'common cold' virus). This structure, published in 1985, provided important insights into the biology of the virus. These included the *canyon hypothesis*, which described a conserved receptor-binding cleft, hidden from the host immune system, and the presence of a particle-stabilising sphingosine, displaced upon receptor binding. The principles of a metastable virus particle with an antibody-protected receptor-interacting domain are now well established in virology.

The principle of structure informing function was continued in studies of enveloped viruses such as dengue and Zika, the packaging motors of phages that form exquisite molecular machines and the giant Mimiviruses.

These achievements reflected the energy and enthusiasm Michael brought to solving the structures of life and were recognised in accolades from around the world. Michael was a member of the National Academy of Sciences (USA), a Foreign Member of the Royal Society (UK), a recipient of the Gregori Aminoff Prize (awarded by the Royal Swedish Academy of Sciences) and a presidential appointee to the National Science Board (USA).

David J. Evans
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Reviews

Infection Prevention and Control: Perceptions and Perspectives

Edited by Paul Elliott, Julie Storr and Annette Jeanes
CRC Press (2015) £38.99 ISBN 978-184619-989-9

It is no secret that now even the shortest of hospital stays drastically increases your risk of developing a hospital-acquired/healthcare-associated infection (HAI). HAIs are associated with extended hospital stays, high care costs and an increased risk of death for both patients and healthcare facilities worldwide. Infection prevention and control (IPC) is an essential element of patient safety and is the responsibility of all those who provide care.

Whilst not all HAIs are preventable, in many cases they are no longer considered an acceptable adverse event during a hospital stay, especially in the face of ever-increasing antimicrobial resistance. Extensive IPC policies are in place, such as hand hygiene and global antibiotic stewardship. However, as antibiotic resistance begins to surpass novel discovery and development, it is clear that perhaps novel approaches are required, before many aspects of modern medicine are no longer viable.

Typically, publications on IPC focus primarily on the scientific and technical aspects of infection control. *Infection Prevention and Control: Perceptions and Perspectives*, however, introduces a novel way of thinking. The book is wide-ranging and includes the perspectives of not only those providing the care but also of the patient and family, giving a voice to those who receive healthcare and highlighting the key role they also play in infection prevention. It also stresses leadership throughout, emphasising that without effective direction and management at all levels, there can be no further improvements.

Whilst this book is less likely to be suitable for someone lacking a sound background knowledge of IPC, it provides a new and stimulating perspective and would be highly beneficial for those looking to further their professional development.

Helina Marshall
Queen's University Belfast, UK

For more reviews, please visit the online issue of *Microbiology Today* at **microbiologysociety.org/microbiologytoday**.

Comment

Industry insights in drug development

Michael Bagnall

Delivering life-changing medicines within today's bio-pharmaceutical industry is a complex operation informed by early development decisions, and the time, investment and tenacity of our teams is not always visible to our most important stakeholder, our patient. The following short narrative will highlight some of the challenges we face as we transform the lives of millions of patients every day.

Discovery

When considering molecules for drug candidacy in Phase I trials, a bench scientist may not have formed an optimised manufacturing process. However, as we are recognising at Merck Sharp & Dohme (MSD), we need to embed manufacturing considerations earlier on in the development pathway for critical success. We realise that manufacturing technologies are a key corner stone for the successful production of molecules and, as we progress to more bespoke molecules, a number of critical elements need to be addressed as early in the process as possible.

Assume you have discovered a new antibiotic – what next?

Manufacturing costs are often multiple millions of pounds if a bespoke facility is required. Should the molecule in question be for a large-scale public health issue (for example, cholesterol, diabetes) this cost can be offset against the longevity of the commercial lifecycle, essentially recouping the costs over a number of years when the treatment is protected by a patent. Increasingly, however, the molecules identified are for small patient populations and, as we progress further down the path of personalised medicine, this will continue to challenge the bio-pharmaceutical industry. Indeed, one of the biggest challenges we face, antibiotic resistance, is impacted by this scenario. Any new antibiotic will, by definition, be highly restricted on use to inhibit further resistance mechanisms. In prescribing this business model, the pressures on the associated manufacturing costs would be significant and could slow progression to market.

Commercial supply

In order to combat manufacturing costs, Contract Manufacturing Organisations (CMOs) are often used. These CMOs offer a platform of manufacturing operations from high-potency powder handling, sterile containment for primary container closure, through to full co-packed combination product. Here the issue is now one of capacity. Given the financial constraints highlighted, there are ever-increasing demands for CMO manufacture; these by nature are specialised and, as such, a very small pool of manufacturing companies exists.

Sterile bottles on the bottling line of a pharmaceutical plant. Neznam/iStock

Consider your antibiotic; this has been refined to a sterile powder formulated into sterile cartridges for an auto injector. There is a minimal list of potential suppliers, assuming a platform existed. Once secured, the manufacturing plan will need to be negotiated. Typically, these types of platforms offer total capacity of hundreds of millions of units per year. If we look to supply a Phase III clinical study, we could need a fraction of this (2,000–5,000 units) and for a restricted-use antibiotic the commercial volumes will continue to be low, meaning we are just a small part of the CMOs' 'book of business'.

Regulatory landscape

The regulatory landscape has never before been so dynamic and demanding. With the onset of the US Food and Drug Administration (FDA) Medical Device and Combination Products legislation and the European Union Medical Device Directive (MDD), the path for any new delivery system and active pharmaceutical ingredient (API) is much more complex. A device (bespoke or platform) will require a design history file or technical manual if a CE mark is mandated. These regulations increased following the Poly Implant Prothèse (PIP) breast implant recall in 2010, including human factor testing, user harms assessments and toxicology requirements to name a few. Combined with the traditional New Drug Application (NDA) requirements, these are built into MSD's drug/device development to ensure our products are safe and effective.

When a fully-approved product is ready for market, the constraints built in at the beginning of drug discovery then play a critical role in the agility and responsiveness of supply.

Key constraint considerations

What is the demonstrated product stability? What manufacturing requirements do we have? Explosive risks associated with powders? Cold chain storage? Light protection? Sterile barrier breakdown? Analytical release methods? Import analytical methods? Provision of inputs? A casual look at this list may seem overwhelming, a missed step here would be a costly mistake.

Consider influenza vaccine production – global production of egg-based flu vaccine is constrained by the number of eggs available. Consider a temperature-sensitive oncology therapy held incorrectly at an airport to allow complex final product import testing to be conducted, rendering the shipment useless as the product is now ineffective. Both scenarios restrict product availability for our patients.

Supply chains are the mechanism for getting our medicines to our patients. I have offered an insight into this increasingly complex and globally dispersed operation in order to highlight the challenges faced and how these, if considered early, can be overcome.

Despite the challenges, we must continue to innovate for our patients and deliver life-changing medicines from the drug discovery lab bench through to the end of the supply chain.

Michael Bagnall

Virtual Plant Manager – External Manufacturing Operations, Manufacturing Division, Merck Sharp & Dohme Limited, Registered Office Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

e michael.bagnall@merck.com

Living with his wife and daughter in the Peak District, Mike graduated from University of Wales (Aberystwyth, UK) in 2004 with a BSc in Microbiology. Mike has 15 years' pharmaceutical operations experience, from drug development to full-scale commercial production/plant management. Now working within MSDs External Manufacturing Team, Mike manages the external production at various vendor factories globally.

On a typical day (or week) in your position what do you do?

A typical day as a Virtual Plant Manager is anything but typical! A day might start with releasing production orders for my CMO to produce, ratifying and approving the five-year production plan. There may be a team meeting with my focus factory to understand the quality, technical and operations tasks needed in the short term. Other tasks may include switching to a production schedule review with the CMO, Brexit planning, trade dispute oversight (for supply chain disruption), invoice approvals, strategic project review meetings, to name a few. It's certainly never, ever dull.

What inspired you to become a microbiologist?

When you consider that a small bundle of fairly simple proteins, lumped together, can either kill you or produce an antibiotic that saves billions, it's easy to be inspired! I wanted to understand this world in all of its wonderful complexity.

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