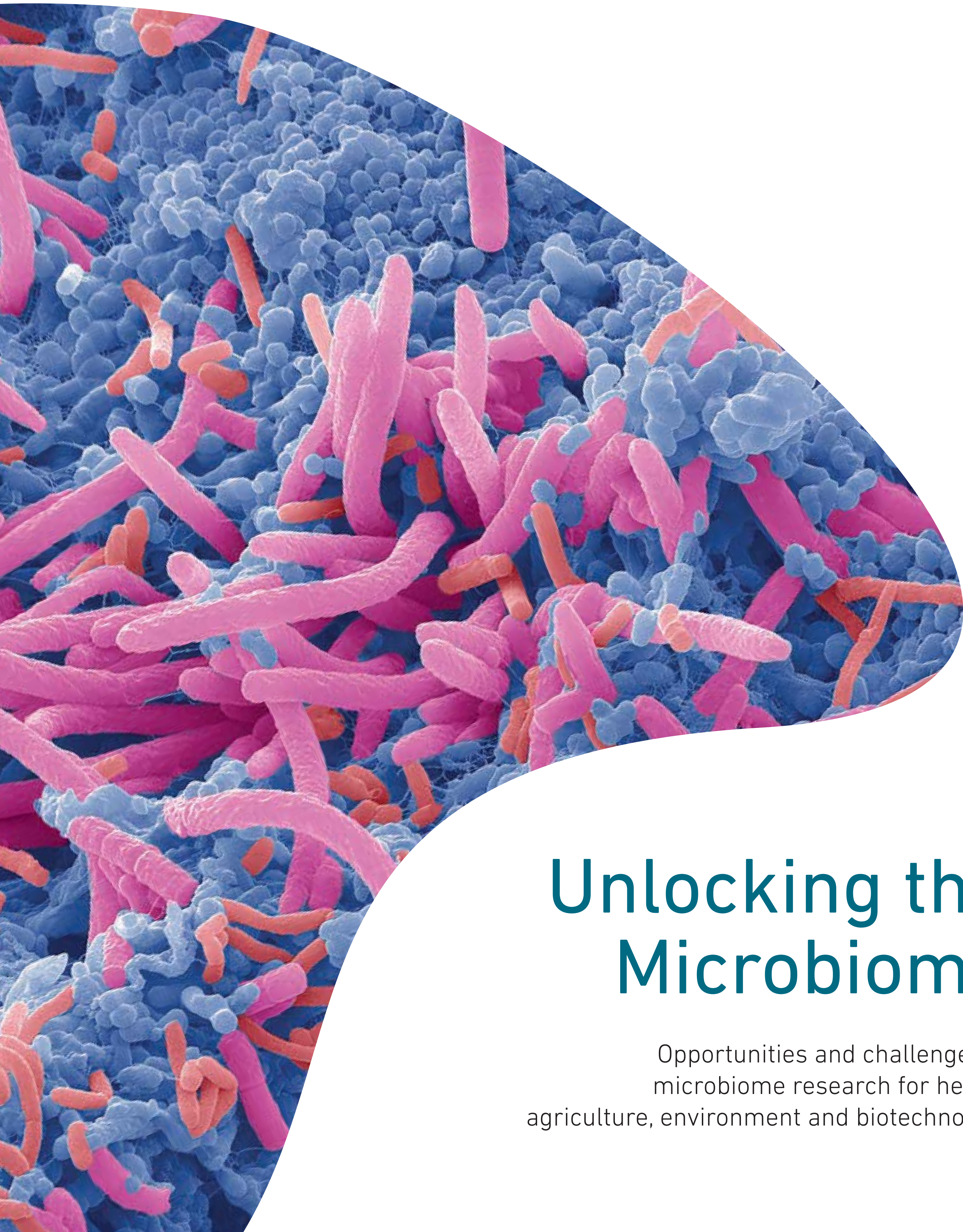

Unlocking the Microbiome

Opportunities and challenges of microbiome research for health, agriculture, environment and biotechnology

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Front/back cover Coloured scanning electron micrograph of bacteria on the surface of a human tongue.
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Foreword

There is a real excitement in microbiology at the moment and it revolves around the area of microbiome research. While microbiomes have always been with us, and have always played fundamental roles in how different systems function, we did not have a specific name for them until quite recently, and we have only recently started to explore them in large numbers as technology now allows us to capture – at different 'omic' levels, such as genomes, transcriptomes and metabolomes – a whole microbiome and its microbiota and metagenome.

While we all have a personal interest in understanding human microbiomes and how they influence health and disease, in the wider arena environmental microbiomes are fundamental to global ecosystem functions, services and life. All of the major global geochemical cycles, for example the nitrogen cycle, would fail if specific microbiomes, which are responsible for key steps within the cycle, were perturbed in such a manner that they did not fulfil their evolved roles. Using a microbiome-led approach will help us understand where we need to invest our efforts to ensure that these environmental cycles continue to support an ecosystem conducive to life.

In this policy document, we have explored the importance of these microbiomes to the economy and society. We currently stand on the verge of an exciting new era in microbiology in which we have the potential to fully define the importance of microbes in supporting microbiome function, while determining how we can modulate this to maintain its beneficial effects and improve them or even restore them when we have destroyed them.

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1. Executive Summary

Our planet is covered with bacteria, viruses, fungi, protists, archaea and algae that are collectively referred to as 'micro-organisms' or 'microbes'. Although invisible to the naked eye, these microbes play key roles in health, food security, agriculture, industry and the environment. Microbes drive global processes that help to support all life on Earth – recycling nutrients needed by crops, breaking down pollutants and providing much of the oxygen we breathe. The microbes hosted by humans and other animals are important for health, disease and nutrition.

Different species of microbes form diverse and complex communities, and when they are combined with a host or environment, we call them microbiomes. Microbiomes have properties that cannot always be predicted from a knowledge of the individual constituent organisms.

All humans, other animals and plants host microbiomes on their surfaces and internally, for example the root microbiome or the skin or gut microbiome. Soils, oceans and buildings also have diverse microbiomes. There is increasing evidence that the composition of microbiomes affects our lives in many ways, and that a deeper understanding of how they work could revolutionise aspects of medicine, agriculture, industry and a wide variety of other crucial sectors.

Despite their prevalence and importance, it is only in recent years that we have begun to develop the techniques needed to study in detail how they function. New science is beginning to open up the potential of managing and manipulating microbiomes. Approaches include introducing beneficial microbes through probiotic food supplements, changing the gut flora by faecal microbiota transplantation, or using disease antagonists; managing environmental conditions to promote useful functions of microbiomes; using synthetic biology to design microbiomes with particular functions; advancing diagnostic and predictive capabilities in health and other sectors; and mining microbiomes as sources of new products.

To help the microbiology community to consider how it might best take advantage of the opportunities stemming from microbiome research, the Microbiology Society convened an international working group of experts from a range of relevant disciplines to survey and analyse the current state of evidence and bring forward some recommendations. To inform the discussions, the Society organised a series of interactive workshops involving 160 participants from the community of researchers, funders, regulators, users and potential users of microbiome research.

This report summarises the view of the working group and the wider community that there are many opportunities both for the advancement of scientific knowledge about microbiomes and for the useful application of that knowledge. The science of microbiomes is highly interdisciplinary and some of the opportunities arise at the boundaries between different fields. Capitalising on the opportunities and delivering tangible benefits to society will depend on a number of interrelated processes, some relying on the approach that funders take, and others dependent on the attitude of regulatory bodies and government agencies. But perhaps the most important outlook is that of the scientific community at large, including the Microbiology Society itself, and its need to take a coordinated and constructive approach. Strong funding and well informed regulation are dependent on transparent and rigorous scientific input, and they will not on their own unlock the potential of the microbiome. Among the recommendations are several for the research community. They call on different parts of the research community in the public and private sectors to work together in sharing data, skills and expertise, crossing disciplinary boundaries, and building effective communities. If this approach can be embedded in microbiome research, the potential benefits will be huge.

2. Recommendations

Building the Evidence Base

1. Researchers should work with funders to enable support for large-sample and longitudinal studies so that researchers can validate associations, identify biomarkers and assess the long-term implications of human or environmental changes to microbiomes.

Interdisciplinary Research and Knowledge Exchange

2. In order to optimise the benefits of this important area of research, which is inherently interdisciplinary, funders and learned societies should work together to facilitate community-led collaborations that are:
   - Multidisciplinary – joining disciplines such as microbiology and biochemistry with clinicians, social scientists and a wide range of other professionals.
   - Cross-cutting – linking experts in human, animal and environment microbiomes.
   - Effective at local, national and international levels.

Building Research Capacity

3. Recognising the central importance of research related to microbiomes, and the specific skills required to maximise its potential, science educators need to develop targeted early-career training and education in areas such as bioinformatics and basic microbiology skills.

4. The scientific community should support workshops, training networks and infrastructure for established research groups to develop and gain access to required resources.

Sharing Data and Resources

5. All relevant sectors of the scientific community should commit to collaborating to establish rigorous standards for data access and interoperability.

6. Funders and the research community should discuss how to effectively and efficiently manage data for the long term, so that maximum benefit can be derived from well-maintained and curated databases.

Best Practices and Standards

7. The international microbiome research community, funders, publishers and regulators should work together to agree standards.

Facilitating Translation

8. In order to accelerate translation, public- and private-sector research funders should focus on facilitating academic–industry collaborative networks, such as BBSRC Networks in Industrial Biotechnology and Bioenergy (BBSRC NIBB) and Science Foundation Ireland Innovation Centres.

9. In order to facilitate translation whilst ensuring consumer protection, policy-makers and regulators should prioritise closer and earlier collaboration with end-users to ensure the development of appropriate regulations for microbiome interventions and products.

Microbiome Research and Society

10. Those involved in microbiome research should work with policy-makers, educators, journalists and the public to ensure that the potential of this emerging science and innovation is communicated accurately, people are enabled to make informed decisions and scientists are always regarded as a trusted source of information.

Nanopore sequencing of DNA.
© Patrice Latron/Eurelios/Look at Sciences/Science Photo Library

3. Microbiomes

Microbes do not live and function in isolation. They form diverse and complex communities associated with specific habitats or niches, with each member playing a particular role that contributes to the community as a whole. When these communities are associated with a host tissue or a particular environmental niche, we call them **microbiomes**, and they have properties beyond those of the individual species of microbes of which they are made up.

The microbiomes hosted by all humans, other animals and plants are important in health, disease and nutrition. Environments such as soils, oceans and buildings host diverse microbiomes. We also utilise microbiomes in a wide range of industrial processes, such as biofuel and food production and water treatment.

Microbiomes can be complex, and often contain distinct sub-communities within a larger whole. They are not static and change in response to external factors. The human microbiome comprises all the micro-organisms associated with a person, but each area of the body has its own specific microbial community – the microbiome of the skin is very different from that of the gut, which is different again from that in the vagina. The collective genetic diversity of all the different microbes in a microbiome can be vast, and many may not be culturable. The microbiome of the human gut, for example, is estimated to include more than 10 million genes in the bacteria alone, around 500 times the number of genes in a human cell.

Scientists studying these microscopic ecosystems investigate the different microbes living in an environment (sometimes referred to as the **microbiota**), their combined collective genetic material in each organism's genome (also known as a **metagenome**), the distinct biological, chemical and physical conditions in which they live and with which they interact, and how they change over time.

By studying the diversity and function of microbes in their own environments and the factors that affect them, scientists aim to uncover the role they play in human, animal and plant health, and in the environment.

It is only in the last few years that we have had the tools to study whole microbiomes, their microbiota and metagenomes, across time and among multiple samples. With the falling cost of DNA/RNA sequencing and other new technologies, we can begin to peel apart the genomes, transcriptomes and metabolomes, and understand in a holistic way how microbiomes engage with the rest of their ecosystems. Work such as the Human Microbiome Project, the TARA Oceans Project, the TerraGenome soil project and the Earth Microbiome Project, have begun to give us that big picture and are providing vast amounts of raw data. Our knowledge and understanding of microbiomes continues to grow, yet research in this field is still in its relative infancy, with scientists only now beginning to understand fully the diversity and functions of these complex ecosystems.

4. Why does microbiome research matter?

Microbiomes are a vital part of the Earth's biodiversity. Research on microbiomes in humans, animals and plants shows that they are intrinsic to our health and that in coevolving with microbes we have effectively outsourced to them some key metabolic functions, such as those involved in nutrition, development, and protection from disease. Microbiomes are fundamental to key geochemical processes – such as the nitrogen cycle, on which life on earth depends – so understanding the microbiome will be crucial to understanding and meeting the challenges of environmental change.

Scientists are beginning to investigate how to manage microbiomes for our advantage. Interdisciplinary approaches combining genomics, microbiology and scientific modelling have allowed the development of predictive models to identify biomarkers and diagnostics that help us monitor and manage microbiomes and can inform microbiome interventions. Examples of approaches being explored to manage and manipulate microbiomes include:

- Introducing beneficial microbes into microbiomes, for example through probiotic supplements, changing the gut microbiota by faecal microbiota transplantation, or using disease antagonists or inoculants employed in agriculture.
- Managing environmental conditions to promote beneficial microbiome diversity and function.
- Using synthetic biology to design microbiomes with a particular function.
- Developing diagnostics, predictive models and biomarkers – with applications from predicting diseases to monitoring the health of water sources and soil.
- Prospecting microbiomes as sources for new products – such as in research to identify new antimicrobials from deep-sea sponges or the stomachs of ruminants.

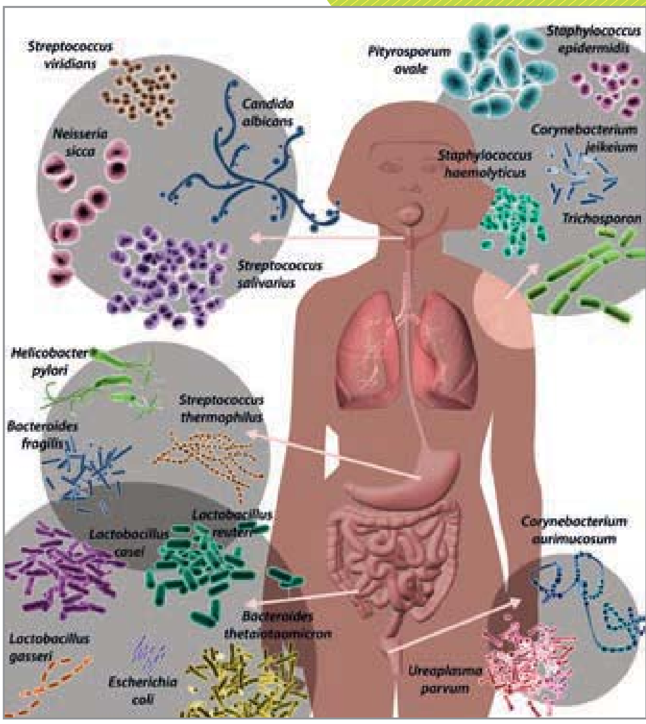
Much of this research is at an early stage – in many cases we are only just beginning to understand the connections between microbial populations within communities and their functions. However, with sustained investment and effective multidisciplinary work, microbiome research has the potential to deliver vitally important advances in multiple areas central to our society and economy.

4.1 Human health

Microbiome research is changing our perception of human biology – where previously we would have thought of this in terms of how our genome interacts with the environment, we now must include the metagenome of the microbes with which we have coevolved. There is increasing evidence that gut microbiomes in particular are fundamental to the **health and nutrition** of humans and animals. Many of the essential metabolites in the human bloodstream on which our immune cells depend are made by microbes in the gut. There is still much research to be done to understand the functional links between the microbiome and disease, but this work is opening up a vast range of opportunities in human health, such as:

- Developing biomarkers from the oral, lung or gut microbiome to identify early risk factors and diagnose diseases such as chronic obstructive pulmonary disease and type 2 diabetes.
- Using faecal microbiota transplants (FMTs) to rebalance the gut microbiome, a technique already proven to be extremely successful in tackling *Clostridium difficile* infections.

Computer illustration of the human microbiome showing various different types of bacteria commonly found on human skin and the linings of organs. © Gunilla Elam/Science Photo Library



- Developing probiotics and prebiotics to restore the balance of microbiomes and treat conditions such as urinary tract infections, diarrhoea, chronic liver disease and potentially even obesity and mental health conditions such as stress and depression.
- Modulating the impacts of chemotherapeutic drugs and developing alternatives to antibiotics.
- Investigating opportunities for personalised or stratified medicine and nutrition.
- Understanding how the gut microbiome influences our ability to respond to many drugs.

Antimicrobial resistance

Antimicrobial resistance (AMR) is a global challenge[1], and a better understanding of microbiomes is one way that we can begin to address it. An increasing number of harmful microbes (pathogens) are becoming resistant to antibiotics and other antimicrobial drugs, resulting in difficult-to-treat infections that threaten public health and lead to economic damage through increased healthcare costs, lost productivity and the loss of livestock and plant products. AMR is also a One Health issue, as resistant microbes and resistance genes can be transmitted between microbes in the microbiomes of humans, animals, plants and environments such as soil and water sources. There is a real opportunity for multidisciplinary microbiome research to contribute to tackling this challenge. Research opportunities include:

- Studying the structure and function of microbiomes to see how antimicrobial drugs affect them and how this relates to the evolution and transmission of AMR.
- Screening microbiomes for novel microbial compounds that could be used to develop new antimicrobial drugs.
- Metagenomic analysis to track the transmission of antimicrobial-resistant pathogens in different environments, from soil to human and animal guts.
- Utilising improved knowledge of microbiomes to develop alternative interventions and therapeutics to antimicrobial drugs, such as probiotics, and new diagnostics, which could reduce reliance on antimicrobial drugs in humans and animals.
- Employing metagenomic tools to detect the presence of superbugs in hospital environments and to inform infection control measures and even hospital building design.

1 Microbiology Society (2017). *Antimicrobial Resistance Policy Briefing www.microbiologysociety.org/uploads/assets/uploaded/f0bed414-2422-459b-b188c766c8de2b0d.pdf*

Tractor cultivating field at spring.
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4.2 Agriculture and food

Microbiomes associated with crops, livestock and agricultural environments are essential for **food security and safety** – for example, microbes in and around plant root systems, the rhizosphere, play a role in plant growth, nutrient absorption, disease resistance and soil structure. Microbiomes involved in processes such as fermentation of beer and cheese create many of the distinctive flavours and qualities of local produce[2]. And the microbiomes associated with food production, storage and transport can be implicated in food spoilage and the spread of pathogens. Microbiome research is uncovering new ways to improve agriculture and food productions, such as:

- Developing high-sugar grasses for animal feeds, to optimise meat production while limiting emissions of greenhouse gases.
- Promoting crop–microbe associations that maintain soil quality, increase yield and provide protection against environmental stresses and pathogens.
- Bioengineering symbioses – for example using microbes to bring the nitrogen-fixing and soil-enhancing benefits of legumes to cereal crops; some of these may potentially be implemented reasonably soon while others are some way off.
- Inoculating plant–soil microbiomes with beneficial microbes to promote health and growth.
- Using whole-genome sequencing and new on-site technologies to rapidly trace the source and cause of foodborne disease outbreaks.
- Screening the rumen microbiome for novel antimicrobials.

4.3 Environment

Microbiomes in the soil and oceans play fundamental roles in numerous ecosystem processes essential for all forms of life on Earth, for example cycling of nutrients such as carbon and nitrogen. Man-made environments, such as buildings and vehicles, have their own microbiomes with important effects on disease transmission and human health.

Human activities and environmental changes are impacting on the diversity and function of microbiomes, with serious implications. By better understanding the impacts of environmental factors on microbiomes and their resilience to change, scientists may make significant contributions to restoring or managing important microbiome functions. For example, scientists are investigating:

- How climate change affects environmental microbiomes in soils, oceans and glaciers, and whether this will accelerate their contribution to greenhouse gas emissions.
- The role of the soil microbiome in transmitting pathogens and the spread of antimicrobial resistance.
- How the microbiomes of surfaces in hospital encourage pathogen transmission, with a view to improving infection control.
- The potential exploitation of marine microbiomes for biotechnological applications[3,4] – possibilities include extracting new antimicrobials from deep-sea sponges.

2 *Although such processes are usually dominated by a single species, there are generally other organisms present, which constitute a microbiome.*
3 INMARE Consortium. *Industrial Applications of Marine Enzymes. www.inmare-h2020.eu/ Last accessed 16 October 2017.*
4 MaCuMBA. *Marine Microorganisms: Cultivation Methods for Improving their Biotechnological Applications. www.macumbaproject.eu/ Last accessed 16 October 2017.*

4.4 Biotechnology

Microbiome research is also an opportunity to help develop the bioeconomy. For centuries, micro-organisms have been harnessed for a wide range of industrial, pharmaceutical and environmental biotechnologies, including the production of drugs, food, drink and biofuels, water treatment and bioremediation of waste and pollutants. Scientists are now employing new tools to better understand, monitor and exploit microbiomes to optimise existing processes to improve quality, productivity and safety, and to develop wholly new processes. For example, UK and Irish researchers are investigating how microbial communities could be used more effectively to convert waste into biofuel and bioenergy, and treat waste water.

Microbiomes and the associated metagenomes potentially offer untapped resources for the discovery of new products of potential industrial, agricultural or biomedical use. Scientists and industry are bioprospecting microbiomes, including human and animal guts, soils and oceans, and associated databases of genomic and protein data, with the aim of identifying novel microbes, compounds and enzymes of potential use for a wide variety of applications.

Opportunities currently being researched include:

- Using microbial enzymes for industrial processes, fine chemical production and environmental clean-up applications.
- Developing bio-refineries for the production and recovery of chemicals, pharmaceuticals, textiles, biodegradable plastics, nutrients and fertilisers from sustainable sources.
- Improving anaerobic digestion processes already used for the treatment and recycling of water, sewage and industrial waste, and more efficient use of methane as a fuel.
- Optimising processes for the production of bio-fuels and bio-energy.
- Identifying novel genes or 'biobricks' for synthetic biology applications.

Biogas plant on a farm. Scientists are investigating livestock microbiomes, and also microbiomes involved in anaerobic digestion to produce biofuels. © CreativeNature_nl / Thinkstock

5. Progressing microbiome research and innovation

Our knowledge of microbiomes is at an early stage. To build on this, scientists will need to continue to develop their research, and to build links between different disciplines, they will need sustained investment to identify and target knowledge gaps, and it will be important to create co-ordinated strategic programmes that link disciplines together to address fundamental aspects of the microbiome.

To gain a better understanding of this rapidly developing area of science, the Microbiology Society convened an Expert Working Group and ran a series of workshops in the UK and Ireland that collectively brought together around 160 microbiome researchers from different fields, along with representatives from industry, funders and government agencies. While experts were clear that developing microbiome research offers opportunities across many areas, they identified a number of challenges to be addressed if we are to maximise the potential benefit that this emerging area of science can have for human health, food security, the environment and industrial biotechnology. In this section, we outline the challenges and opportunities highlighted by experts and their recommendations to progress microbiome research.

Investing in microbiome research

Microbiome research has been attracting international attention from policy makers and research funders, for example:

- In 2016, the White House Office of Science and Technology Policy announced a National Microbiome Initiative to develop microbiome science in the United States, including $121 million of Federal funding in addition to $400 million from non-government groups such as universities and the Bill and Melinda Gates Foundation.
- A European Commission analysis of CORDIS and the EU Open Data Portal identified that between 2007 and 2015 the European Commission's FP7 and Horizon 2020 research and innovation programmes funded 535 microbiome-related projects at a total cost of €1.4 billion. The European Commission also launched the International Bioeconomy Forum in October 2016, which will initially focus on microbiome research and innovation in relation to food and nutrition.
- Both the UK and Ireland have been active in European microbiome research. In Ireland the APC Microbiome Institute is a key centre for microbiome science. In the UK there has been no large-scale strategic microbiome science funding initiative, though the Research Councils and InnovateUK have collectively invested in a diverse range of relevant projects[5]. The BBSRC, together with other partners, has also invested £75 million in the Quadram Institute for Food and Health Science, and one of its key research themes is the gut and its microbiome[6].
- In June 2017, Cancer Research UK launched the next round of Grand Challenges – a series of £20 million awards seeking international, multi-disciplinary teams willing to take on the toughest challenges in cancer – including one to 'Improve treatment responses by manipulating the composition and status of the microbiota'.

5.1 Building the evidence base

Microbiomes are inherently complex and dynamic. For example, although there are broad similarities in the functions of the human gut microbiome, no two people have identical microbial communities, and these vary in different parts of the gut and over a person's lifetime. Other microbiomes are equally varied, while some are characterised by relatively low diversity (for example the vaginal microbiome), and there is no one-size-fits-all description of a microbiome. In addition, complex interactions occur within and between microbiomes and their hosts and environments, and this presents a major challenge in developing knowledge and applications.

5 Research Councils UK and Innovate UK. *Gateway to Research search query 'microbiome OR metagenomics'. http://gtr.rcuk.ac.uk/search/project?term=microbiome+OR+metagenomics Last accessed 16 October 2017.*

6 BBSRC (2016). *The Quadram Institute, a New £75M Food and Health Research Centre. www.bbsrc.ac.uk/news/policy/2016/160215-pr-quadram-institute-new-food-health-research-centre/.*

Coloured scanning electron micrograph of soil bacteria. Soil micro-organisms are vital for nutrient cycling and soil health.
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The majority of microbiome research so far has focused on profiling the taxonomic and genetic diversity of microbiomes and identifying associations with, for example, particular diseases or ecosystem services. This is valuable, but at the same time we need to increase our focus on hypothesis-driven functional and mechanistic research studies to validate and understand the associations that have been found, and to better understand the activities, dynamics and resilience of microbiomes.

We need to establish what is correlation and what is causation. For example, many gut microbiome studies in humans and animal models (many in mice) have observed correlations between changes in the microbiome and disease. However, determining whether these changes are a cause of a disease, or are instead a result of the disease (or even coincidental), is a key challenge that requires fundamental research into mechanisms and outcomes.

In addition to this, there is currently no consensus as to what constitutes a 'normal' or 'dysfunctional' microbiome, or even if such categorisation is possible. While this will clearly be challenging due to the huge variability in microbiomes and environments, validated biomarkers and baseline data are a key need in order to progress research, develop diagnostics and develop and monitor interventions.

Recommendation 1
Researchers should work with funders to enable support for large-sample and longitudinal studies so that researchers can validate associations, identify biomarkers and assess the long-term implications of human or environmental changes to microbiomes.

5.2 Interdisciplinary research and knowledge exchange

Microbiome research is inherently interdisciplinary and requires collaboration, integration of skills and sharing of best practice across many areas, including microbiology, bioinformatics, mathematics, biochemistry, immunology and ecology. It is also important to foster greater knowledge exchange between scientists working on different microbiomes, such as those in humans, animals, plants and the environment, as the fields face many of the same core challenges.

It is not just nationally that interdisciplinary research on the microbiome should be promoted. Research is a global endeavour and microbes and microbiomes do not respect or recognise international borders. Unravelling the complexity of microbiomes and translating this knowledge into new products and interventions will require collaboration across these different disciplines and research groups around the world.

There are examples of good practice. In the UK cross-research council funding on antimicrobial resistance[7] is an area where targeted funding has helped promote interdisciplinary research. The Biotechnology and Biological Sciences Research Council (BBSRC) has also identified integrative microbiome research as a responsive mode priority to address key knowledge gaps. Internationally, developing interdisciplinary research is also a focus of the US National Microbiome Initiative. Despite these examples, our working group felt that different disciplines and work on different microbiomes too often still operated in silos. They argued that better support for interdisciplinary research was vital to developing our fundamental understanding of microbiomes, addressing knowledge gaps and facilitating translation.

Interdisciplinary research can be challenging and requires new ways of thinking and working, as well as training, skills, funding and publishing mechanisms that promote and acknowledge these projects. However, the potential benefits from improved interdisciplinary working, both for accelerating the work of scientists and for enhancing the applications for society, are enormous. Targeted interdisciplinary networks, training and funding are essential to facilitate integrative research.

Recommendation 2
In order to optimise the benefits of this important area of research, which is inherently interdisciplinary, funders and learned societies should work together to facilitate community-led collaborations that are:

- Multidisciplinary – joining disciplines such as microbiology and biochemistry with clinicians, social scientists and a wide range of other professionals.
- Cross-cutting – linking experts in human, animal and environment microbiomes.
- Effective at local, national and international levels.

5.3 Building research capacity

Our working group and workshops identified a number of significant skills and expertise gaps amongst researchers that were a hindrance to microbiome research. This was an issue for both established and early-career researchers. These gaps included:

- Bioinformatics – this is insufficiently covered in undergraduate and PhD programmes, and often not represented in peer review panels, leading to a downstream skills gap in what is a vital area for microbiome research.
- Basic microbiology – including expertise in traditional and emerging culturing approaches, microbial physiology, design and interpretation of metagenomics projects, and microbial ecology. Shortages in these skills are impeding translation and the application of advances in microbiome knowledge in areas such as the water industry.
- Integrated approaches – for example, integrating genomics and other types of data, and linking bioinformatics with underlying microbiology.
- Taxonomically diverse approaches – which effectively integrate knowledge about bacteria, viruses, fungi, algae, protists and other microbes.

7 MRC. *Tackling AMR – A Cross Council Initiative. www.mrc.ac.uk/research/initiatives/antimicrobial-resistance/tackling-amr-a-cross-council-initiative/ Last accessed 16 October 2017.*

Recommendation 3
Recognising the central importance of research related to microbiomes, and the specific skills required to maximise its potential, science educators need to develop targeted early-career training and education in areas such as bioinformatics and basic microbiology skills.

Recommendation 4
The scientific community should support workshops, training networks and infrastructure for established research groups to develop and gain access to required resources.

5.4 Sharing data and resources

Generating microbiome data is relatively straightforward, and is rapidly becoming more affordable, although data analysis is resource-intensive. In 2012, sequencing the genomes of all the microbes within a soil sample cost around £80,000; currently, the same work would cost about £2,000. A single metagenomic project might involve sequencing thousands of microbiome samples and produce huge volumes of data – the sequences of over 150 billion genes and gene fragments are stored by the European Bioinformatics Institute alone – so standardisation of datasets, infrastructure and careful storage management are important if researchers are to be able to effectively share, access and use these 'big data' sets.

It is important that researchers can easily access well-maintained, integrated genomic datasets – these are essential resources that facilitate microbiome research. There are some positive examples upon which to build, where platforms for microbial genomics have been improved – for example the European Elixir project to develop resources to handle data, and the Medical Research Council Cloud Infrastructure for Microbial Bioinformatics (MRC CLIMB), which provides free microbial informatics storage and analysis tools for microbiologists in the UK.

In order to handle the wealth of data being generated, scientists have emphasised the need for:

- Improved data quality, access, integration and infrastructure.
- More robust and higher quality databases, with improved interoperability between datasets and easier sharing of data.
- Development of biobanks for microbiome samples, and improved access to existing biobanks for microbiome samples.

Recommendation 5
All relevant sectors of the scientific community should commit to collaborating to establish rigorous standards for data access and interoperability.

Recommendation 6
Funders and the research community should discuss how to effectively and efficiently manage data for the long term, so that maximum benefit can be derived from well-maintained and curated databases.

5.5 Best practices and standards

Developing best practices and standards for sampling, analysis and data collection is essential for robust microbiome research, given the large variability and the need to compare and combine datasets. Without standardisation there are serious limits to reproducibility and comparison between studies, and to the ability to validate potential links between disease and changes in the microbiome. This has been identified by scientists as a barrier to advancing research, particularly when trying to validate potential links between disease and changes in the human microbiome.

Standard operating practices also have an important role to play in the development of regulatory frameworks to enable commercialisation, for example to reliably assess novel microbiome therapies, tools or products. Robust agreed standards will therefore both support basic research by giving greater authority to results, and also facilitate more rapid translation into commercially available products and therapies.

There is a need, however, to balance the requirement for standards against the need to enable new discoveries and account for rapid advances in technology, which may mean that methods become outdated quickly. In addition, determining what the best standard protocols are presents a challenge due to the inherent complexity and variability of microbiomes. It is important that these issues are considered early on in research through close collaboration between researchers, funders and regulators.

Recommendation 7
The international microbiome research community, funders, publishers and regulators should work together to agree standards.

An artificial gut, which can be used to study some aspects of the human gut microbiome.

5.6 Facilitating translation

While there is huge potential for developing microbiome research, there are also challenges to facilitating translation from basic research to the development of new products and therapies. A key challenge identified is around regulation. Potential areas for clarification include:

- Whether human microbiome samples should be treated in the way same as human tissue samples for regulatory and ethical purposes. This has the potential to be a hindrance due to issues relating to donor permissions and the UK Human Tissues Act.
- Concerns that the Convention on Biological Diversity Nagoya Protocol on Access and Benefit Sharing of Genetic Resources may lead to issues around securing intellectual property and conducting research that will adversely affect investment and translation. International agreement should be sought on implementation of the Nagoya Protocol in relation to microbiome research.
- The classification and regulatory requirements for agricultural and environmental microbial inoculants and biostimulants are expensive and unclear – using developing scientific knowledge to inform regulation in this area is important to promote translation.
- Regulation of probiotics and nutraceuticals can impede the translation of microbiome research. For example, there can be uncertainty as to whether a product should be regulated as a medicine or as a food, or in demonstrating efficacy, which has implications for the ease and cost of development, safety assessment and consumer protection. There is a need for funding, better design and implementation of trials, as well as a better understanding of the mechanistic links between microbiomes, nutrition and health, in order to be able to validate microbiome foods and medicine.

Translating microbiome research successfully will also involve facilitating knowledge exchange between scientists, regulators, policy-makers and end users of research, to identify priorities and to ensure any resulting applications will be useful in the clinic or in the field. There are already some examples of initiatives to strengthen academic–industry collaboration on microbiome research. For example, in the UK CABI and Rothamsted Research are collaborating on establishing a UK Plant Microbiome Initiative to link industry, academia and other stakeholders with interests in sustainable crop productivity.

Recommendation 8
In order to accelerate translation, public and private sector research funders should focus on facilitating academic–industry collaborative networks, such as BBSRC Networks in Industrial Biotechnology and Bioenergy (BBSRC NIBB) and Science Foundation Ireland Innovation Centres.

Recommendation 9
In order to facilitate translation whilst ensuring consumer protection, policy-makers and regulators should prioritise closer and earlier collaboration with end-users to ensure the development of appropriate regulations for microbiome interventions and products.

Coloured scanning electron micrograph of various bacteria found in a sample of human faeces.
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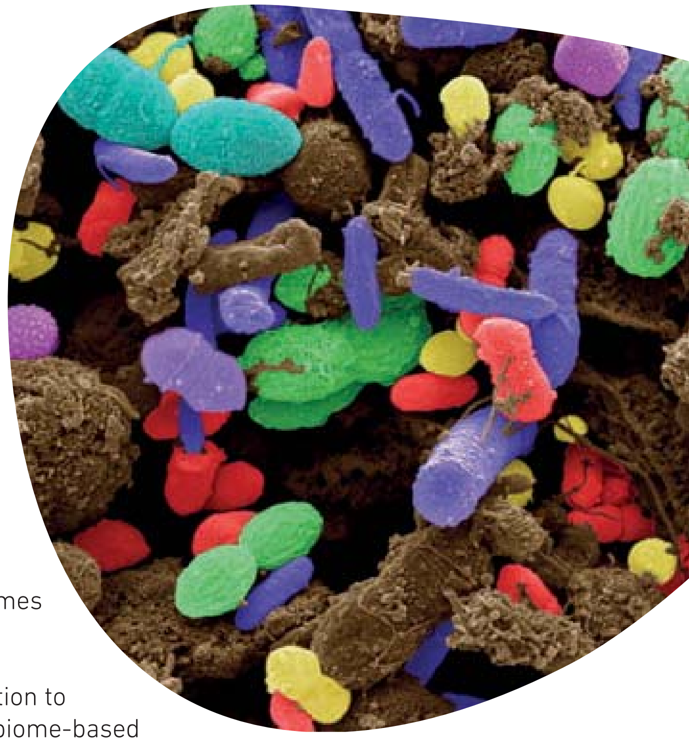

5.7 Microbiome research and society

Interest in microbiome research creates a great opportunity to engage the public and stakeholders about the importance of microbes and microbiology for all aspects of our lives. Greater public engagement will in turn help stimulate interest in science and scientific careers, and enable greater public and policy support for public health initiatives and the development of bioethical standards.

However, while promoting the great promise of microbiome research, as with any emerging area of science, it is important to remain realistic about the potential benefits, to avoid over-hype and consequent loss of interest and public trust.

Some microbiome research and translation raises potential safety and ethical questions, including the untested consequences and long-term effects of manipulating microbiomes for health or the environment; the end-user acceptability of microbiome technologies and interventions, such as synthetic biology or faecal microbiota transplants; and consumer protection to ensure that the public are appropriately informed about microbiome-based products and interventions, such as dietary and life style recommendations and pre- and probiotic products.

Therefore communication about microbiome research needs to be clear and measured, in order to manage expectations and ensure that the public is appropriately engaged and informed, and enabled to make decisions based on the best evidence.

As has occurred in the related field of synthetic biology, it will be important for microbiome researchers to work with social scientists, policy makers, regulators, the media and the public and end users of research to consider the social and bioethical implications of novel microbiome discoveries and biotechnologies. This interaction is a focus of the Interdisciplinary Microbiome Project at the University of Oxford[8]. Citizen science provides another kind of opportunity to engage the public and contribute to microbiome research. Examples of existing projects include the Good Germs/Bad Germs Project[9] and the British Gut Project[10].

Recommendation 10
Those involved in microbiome research should work with policy-makers, educators, journalists and the public to ensure that the potential of this emerging science and innovation is communicated accurately, people are enabled to make informed decisions and scientists are always regarded as a trusted source of information.

8 University of Oxford (2016–2017). *Oxford Interdisciplinary Microbiome Project. www.socsci.ox.ac.uk/research/divisional-research-incubator-themes/interdisciplinary-microbiome-project.*
9 University of Oxford. *Good Germs, Bad Germs. www.goodgerms.org/ Last accessed 16 October 2017.*
10 King's College London and The American Gut Project. *British Gut. http://britishgut.org/ Last accessed 16 October 2017.*

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MICROBIOLOGY SOCIETY

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