

Part of the conference series
Breakthrough science and technologies
Transforming our future

The microbiome: human medicine and agriculture in a microbial world

Conference report
Held on 5 October 2018

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Introduction

On 5 October 2018, leading scientists from across academia and industry attended a conference at the Royal Society to discuss microbiomes and their emerging influences on medicine and agriculture.

It has been increasingly realised that all animals and plants are the sum of not only the products of their own genomes but also of the genomes of the microorganisms that inhabit them and have co-evolved with them from the start of their evolution. This paradigm shift in thinking is leading to many new opportunities in scientific research and application and this conference was held to draw attention to these, their implications for UK science and their translation into commerce.

Studies on various microbiomes have been growing exponentially during this past decade, partly because the costs of DNA sequencing have been reduced substantially, enabling microbes in complex mixtures to be defined by their genomes. The findings have generated knowledge on the roles that populations of microorganisms play in determining human health and also in defining soil fertility, crop performance and defence against diseases and stresses in agriculture.

The conference covered a wide range of topics including the application of microbiome science to agricultural yield, crop resilience in the face of climate change, and greenhouse gas emissions from farm animals. The influence of bacteria on human health, in particular immune-therapy, Inflammatory Bowel Disease (IBD), informatics, and the gut-brain axis, were also explored. Furthermore, the technical, regulatory and ethical challenges associated with commercial applications of this field were highlighted.



Image: Speakers and organisers of the conference.

This conference is part of a series organised by the Royal Society entitled *Breakthrough science and technologies: Transforming our future*, which addresses the major scientific and technical challenges of the next decade. Each conference covers key issues including the current state of the UK industry sector, the future direction of research and the wider social and economic implications.

The conference series is organised through the Royal Society's Science and Industry programme which demonstrates the Society's commitment to integrate science and industry at the Society, promote science and its value, build relationships and foster translation.

This report is not a verbatim record, but a summary of the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society.

Full versions of the presentations can be found on our website at royalsociety.org/tof-microbiome

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“Microbes were on Earth long before the evolution of plants and animals. The higher organisms of today are products of coevolution with microbes, but the scientific communities have not yet done justice to this concept.”

Professor Richard Flavell CBE FRS
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Microbiomes: the translational landscape

Professor Denise Kelly of Seventure Partners opened the conference, describing the current industrial landscape of human microbiome studies, past developments and future prospects.

Over the last decade, there has been considerable progress in understanding human microbiomes and their relationship to human health and disease. In addition, there has been a reinvigorated interest in the importance of microbiomes in animal production and environmental sustainability.

The microbiome market landscape

Awareness of the functions of microbiomes has driven the rapid growth of microbiome-based developments in industry. The current market is predominantly in the pharmaceutical industry (focused on gastroenterology), but growing in agriculture and cosmetics. Today, the rapidly growing interest is illustrated by:

- The establishment of new centres of excellence.
- The exponential growth in publications, patents, and meetings.
- Growing numbers of clinical trials worldwide, with 337 registered trials with 'microbiome' in the title.
- \$1.5 billion of private and public investment.
- Several hundred microbiome start-ups founded since 2013, covering many modalities.
- Buy-in from the pharmaceutical and nutritional industries, including many joint ventures and acquisitions.

The role of the microbiome in human health

Without a definition of the human microbiome in a normal healthy individual it is challenging to define the parameters of an 'abnormal' microbiome. However, the microbiome has been found to have a role in allergies, Inflammatory Bowel Disease (IBD) pathogenesis, and immune-oncology. Current research seeks to understand:

- Transkingdom interactions between viruses, bacteriophage, fungi and archaea.
- Microbe functionality rather than taxonomy eg carbohydrate/protein/lipid metabolism.
- The distinction between healthy symbiotic and unhealthy dysbiotic microbiomes.
- The links between chronic diseases (IBD, autoimmune, allergy, cancer), impaired immunological functions (development, regulation, homeostasis) and microbiomes.
- The links between neurological degeneration and gut-brain connections to Autism, Parkinson's disease and Alzheimer's disease.

To progress further, improved quality control, standardisation and reproducibility of results are required. Microbiome sampling must be extended beyond Europe and North America to see the breadth of microbiome diversity and help identify:

- Microbiomes driving disease states.
- Beneficial therapeutic bacteria in microbiomes.
- Biomarkers for diagnosis/prognosis, patient stratification, and personalised interventions.

Future challenges

Challenges in bringing microbiome-based products to patients and consumers include a need for:

- **Understanding microbiome functionality** to improve discovery and functional screening; mode of action; target validation; humanised preclinical models.
- **Big data platforms** to deduce causality from microbiome surveys and deliver predictive outcomes from multi-omic patient studies.
- **Clinical validation** to overcome regulatory hurdles; develop scalable manufacturing and formulation, robust clinical trial designs and long-term safety strategies.
- **Intellectual property management** to develop large foundational patents and freedom to operate.

These will facilitate development of product modalities including live bio-therapeutic products; medical foods, nutrition additives, pre and probiotics; diagnostics, patient stratification and personalised therapies.



Image: Denise Kelly, Seventure Partners.

“Recognising the roles of microbiomes represents nothing less than a paradigm shift which requires us to reevaluate our understanding of human, animal and plant biology. These kinds of opportunities and shifts come about infrequently. We are living in a very exciting period in a very exciting field.”

Dr Mike Romanos, Microbiotica

“The biodiversity between gut, oral, skin, and vaginal microbiome ecosystems is continents apart and an amazing opportunity for discovery.”

Professor Denise Kelly, Seventure Partners

Understanding the diversity of microbiomes: data driven knowledge discovery applied to the human gut microbiome

Dr Rob Finn of the European Bioinformatics Institute discussed how metagenomic techniques are employed to identify the diversity of microorganisms occupying environments such as the human body, soil and oceans.

Historically, high throughput 16S rRNA amplicon sequencing has been used to catalogue gut microbes, because this marker gene is found in both prokaryotes and eukaryotes. However, this has limited resolution at the species level and recovers only 50% of input genera.

Metagenomic approaches (the analysis of the sum of genetic material from an environmental sample) are beginning to unveil the 'microbial dark matter'. In whole genome shotgun metagenomics, entire genomes are sequenced, retrieving resolution at the species level and giving functional readouts of the constituent bacterial strains that can then be entered into the big data bioinformatics forum.

Recent research using raw DNA sequence analysis indicates the entire population (taxonomy, function) but gives no indication of whether these sequences are from the same organism. Diminishing sequencing costs and improved algorithms now enable grouping of sets thought to be from the same organism, creating a Metagenome Assembled Genome (MAG).

FIGURE 1

Summary of genome sequencing approaches.

	Pros	Cons
Amplicon	Cheaper experimentally and computationally	Lacks resolution and restricted taxonomic range
Whole metagenome shotgun	Overview of the entire sample	More computationally expensive, disconnected between taxonomy and function
Assembly	Genomes, contigs and full length proteins	Only most abundant organisms, computationally very expensive

Source: Dr Rob Finn, European Bioinformatics Institute.



Image: Dr Rob Finn, European Bioinformatics Institute.

Questions to answer in future work

- Is it possible to recognise a core human microbiome worldwide?
- How do human gut microbiomes differ between continents?
- How many MAGs cannot be matched against known reference sequences and therefore represent novel genomes (30% in his study)?

Challenges

As collections are built, the efficiency of analyses will increase. However, many technical challenges remain in the bioinformatics:

- How to deploy and scale in a cloud environment.
- How to predict the amount of memory and CPU time required.
- Workflows that capture all parameters, including informatics and reference datasets.
- Developing and enforcing a common workflow language globally.

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“The nature of the informatics problem that we are trying to overcome in assembling Metagenome Assembled Genomes is like trying to complete thousands of jigsaw puzzles that have been tipped out of their boxes, had pieces removed, and where the pictures are missing.”

Dr Rob Finn, European Bioinformatics Institute

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Precision metagenomics in personalised medicine and early life microbial colonisation

Dr Trevor Lawley of Microbiotica introduced ‘precision metagenomics’, a reference genome-based analysis approach developed at the Human Microbiota Interactions Lab. He also described results from University College London’s Baby Biome Study.



Image: Dr Trevor Lawley, Microbiotica.

A lack of reference genomes has been a barrier to exploiting the microbiome. Precision metagenomics uses mass isolation of bacteria to generate a reference genome sequence database, addressing key bottlenecks in high resolution strain profiling. Compared to 16S sequencing, this technique enables the precise definition of bacterial strains and their functions.

Microbiotica is developing a Personalised Bacterial Bank (PBB) of a single healthy adult to characterise gut bacteria from whole genome sequencing. A full PBB of a healthy adult comprises 200 – 250 species. The aim is to correlate gut microbiota with phenotype for live bacterial therapeutic or biomarker and drug target discovery, and create a reference genome database.

The identification of specific strains in microbiomes facilitates:

- Patient stratification.
- Precise characterisation of microbiota linked to phenotype in clinical studies.
- Discovery of bacterial therapeutics to correct dysbiosis or regulate the immune system.
- Discovery of biomarkers of patient response.

Baby Biome study: microbial colonisation and development in early life

Baby Biome Study aims to correlate early life microbiota development with long-term health. The first 3 – 4 weeks of life are the most important for microbiota: the microbiome is rapidly populated, and this is affected by a baby’s surroundings. Cycles of perturbations caused by intrinsic and extrinsic factors, like vaginal versus Caesarean-section birth, breastfeeding, diet, drugs, and infections, are followed by resistance mechanisms that return the microbiome to normal.

In the UK, 24% of children are born by elective C-section delivery. Perturbed microbial colonisation of babies born in this way predisposes the child to disease in later life, including obesity and asthma. The aim is to understand which factors contribute to this and how they can be changed.

Conclusions from the study to date

- Maternal transmission of microbes is stunted in C-section neonates.
- C-section promotes colonisation by healthcare-associated pathogens.
- Microbiome maturation and assembly look similar for vaginal and C-section born babies, but there is much less *Bifidobacterium* and other pioneering species with C-section, and many more of the species that are normally in the minority.
- Breastfeeding is thought to return the microbiome to 'normal' but this is yet to be confirmed.
- The microbiome and immune system develop in parallel.

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“The four or five phyla that dominate the human microbiome are no accident and are highly evolved to coexist in harmony with us.”

Dr Trevor Lawley, Microbiotica

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Modulating microbiomes for health: host microbiome interactions in health and disease

Professor Eran Elinav of the Weizmann Institute of Science discussed current research within his laboratory to understand three microbiome-mediated treatments. The results provide an opportunity to use DNA sequencing and other tools to develop personalised microbial treatments.



Image: Professor Eran Elinav, Weizmann Institute of Science.

Personalised diets reduce post-prandial glucose response

The standard Glycaemic Index food grading system based on post-prandial blood glucose spikes is used to determine ‘good’ and ‘bad’ foods. In reality, individuals have varied responses to the same foods, likely caused by vastly different gut microbiomes, making a one-size-fits-all diet impossible.

Machine learning algorithms using continuous glucose monitor readings were able to predict an individual’s glycaemic response for any food. From this, ‘good’ and ‘bad’ diets were devised for individuals in a pre-diabetic cohort with the personalised ‘good’ diets successfully reducing the post-prandial glycaemic response. Further sequencing of the participant’s microbiome could be used to corroborate the predictions.

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“The current non-personalised microbiome mediated treatment is being transformed into a more measurement based, science based, and personalised approach.”

Professor Eran Elinav, Weizmann Institute of Science
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Is there a memory of obesity?

Sequential dieting cycles exacerbate post-diet weight gain in humans and this effect is also seen in mouse studies. The gut microbiome is the only factor that does not normalise after a successful diet. Microbiome transfer to germ free mice transmits metabolic memory: when germ free mice received the microbiome of mice that dieted, they were 10% more likely to tend towards obesity than when the microbiome was transferred from mice that were never obese. Signatures of the microbiome could both predict, or be treated to improve, cycling obesity. Bodyweight fluctuations are linked to increased risk of coronary events, making treatments based on the microbiome important for long-term heart health.

Probiotics and microbiome recolonisation

Probiotics are controversial and have been declined by the regulators for medical applications, yet they are globally integrated into many foods, lotions, and baby formulas. A study of the impact of probiotics on gut colonisation revealed two distinct groups. Permissive individuals show significant changes to their host microbiome and host gut transcriptional profile and the microbes colonise in the lower intestinal tract. Resistant individuals do not colonise at all. This response could be predicted for particular probiotic treatments, and would allow personalisation of the approach.

In a second test, probiotics were taken following a course of strong antibiotics: a use suggested by 65% of US family physicians. The microbiome recolonised much faster for the group of individuals taking probiotics than without, but with severe inhibition of the reconstitution of the indigenous microbiome. In contrast, the group receiving auto-faecal microbiota transplantation recolonised their indigenous microbiome within days. Probiotics disrupt the indigenous gut microbiome, its function, and the gut transcriptional profile, and a severely disturbed configuration is maintained.

Gut reactions: immune pathways in the intestine in health and disease

Professor Fiona Powrie FRS of the Kennedy Institute of Rheumatology discussed microbial products that promote innate and adaptive immune responses in the intestine and how these may be exploited therapeutically.

Chronic inflammatory diseases are difficult to treat as they are multifactorial, caused by the interplay of environmental and genetic factors. In IBD there is an aberrant inflammatory response to intestinal bacteria, due to a breakdown in the dialogue between the microbiota and the immune system. Many IBD patients do not respond to treatment and may progress to surgery. There is also an increased risk of colorectal cancer.

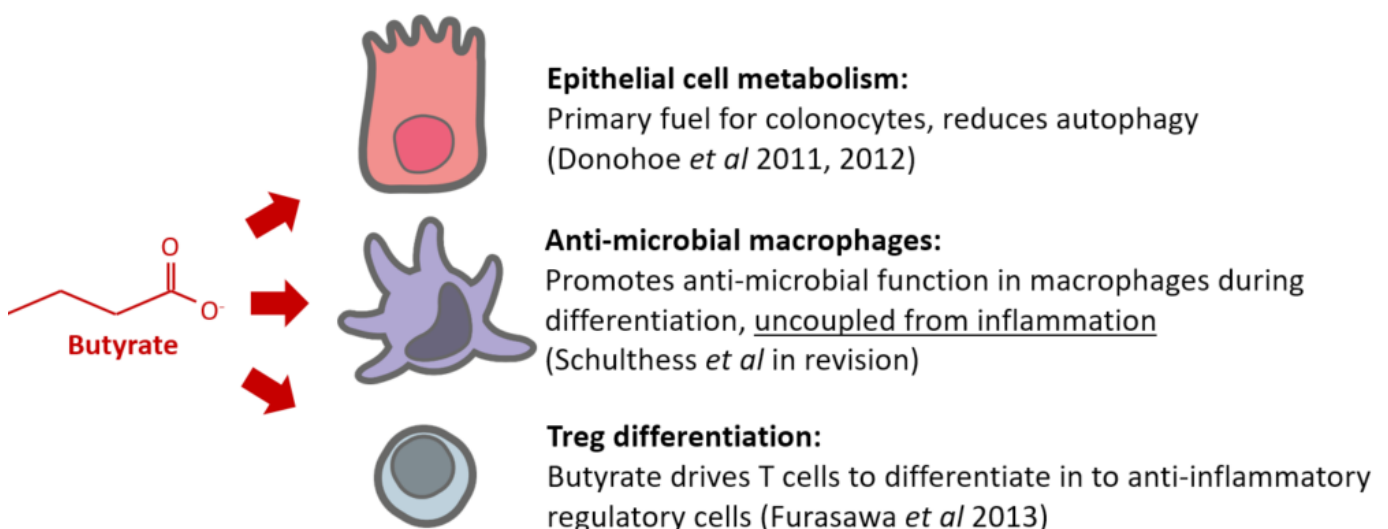
Metagenomic microbiome analysis in Crohn's disease, a form of IBD, shows several taxa are increased, reduced or missing in the disease state, but there is a need to understand which relationships are causal. Greater understanding is also needed in how different bacterial metabolites impact intestinal homeostasis and how deficiencies in these pathways, especially short chain fatty acid biosynthesis, may drive intestinal inflammation.

As regulatory T cells regulate other members of the immune system, there is great interest in uncovering the bacteria and bacterial factors that induce these cells as that may bolster intestinal homeostasis. Recent studies have identified particular bacteria that promote regulatory T cells including the bacterium *Helicobacter hepaticus*.

Fatty acid metabolites have long been known to have important roles in the intestine. Recent studies have shown that the metabolite butyrate alters the differentiation of macrophages to enhance antimicrobial function. These macrophages could have an important role in intestinal homeostasis by killing invasive bacteria ensuring microbes are kept in their place in the gut lumen.

FIGURE 2

Butyrate-mediated effects in the gut.



Source: Professor Fiona Powrie FRS, Kennedy Institute of Rheumatology.

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“Humans must now be considered as a superorganism: the combination of our human genes and microbial residents.”

Professor Fiona Powrie FRS, the Kennedy Institute of Rheumatology

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We are gaining understanding of the host–microbe dialogue at a deep, mechanistic level. Intestinal inflammation indicates maladaptation between host genetics and the microbiome, leading to an inflammatory response that perpetuates itself. Reinstating homeostasis requires a combined approach to inhibit inflammation and correct bacterial balance, promoting production of beneficial products to modulate the host.

There are many opportunities to engineer the microbiome to promote these metabolites, such as influencing dietary polysaccharides and the bacteria present. This fortifies epithelial barrier function, induces the regulatory T cell axis, and promotes antimicrobial macrophages. Ultimately this could lead to a personalised medicine approach based on modulating both microbial and host components.



Image: Professor Fiona Powrie FRS, the Kennedy Institute of Rheumatology.

A new era: development of microbiome drugs for immune related disorders

Dr David Cook of Seres Therapeutics presented clinical and preclinical evidence supporting the development of microbiome-based drugs consisting of groups of commensal bacteria.

Inflammatory Bowel Disease

The microbiome is an attractive therapeutic target for IBD, and there is a microbiome correlate of response in treatment of cancer patients.

The gut contains around 60% of the body's T cells, where they play a central role in immunity. However, there are currently no products that alter the gut lumen, providing an opportunity to develop drugs in combination with existing agents. Dysbiosis in IBD is characterised by reduced *Clostridiales* and increased *Enterobacteriaceae*. Restoring these by faecal transplant shows 20% greater remission than placebo, showing a potential therapeutic role of the microbiome in treating ulcerative colitis.

Anaerobe spores make up the majority of organisms in the human gut and offer a viable mode of treatment as they easily pass stomach acid to reach the gut, and are highly resistant to heat and organic solvents which allows the drug to be purified of other potential pathogens. Remission from IBD after Vancomycin pretreatment and SER-287 (a consortium of bacterial spores) is significantly dose-dependent, where daily treatment induces complete clinical remission in 40% of patients.

Other findings associated with remission are:

- A strong correlation between bacterial species and metabolites that predict clinical remission, indicating the importance of creating a designed ecology.
- A metabolomic signature representing diverse functional pathways, many implicated in IBD.
- Changes in disease-related gene expression.

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"Use of the microbiome as a biomarker to predict who will respond to which drugs could be a profound development."

Dr David Cook, Seres Therapeutics
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Microbiome and immune-oncology

Recent data for solid tumour patients identify a correlation between microbiome composition and outcomes of patients treated with immune checkpoint inhibitors, prompting efforts to evaluate drugs consisting of microbial consortia. Findings include:

- High microbiome biodiversity is associated with better immune parameters and overall survival.
- Reconstituting germ free or immunocompromised animals with a set microbiome composition can inhibit tumour growth.

The current microbiome industry landscape is focused on biologically sourced and fermented bacterial mixtures. Single bacteria strains provide a very different approach, applying a single organism with an important function. Other companies use engineered bacteria, bacterial metabolites, small molecules, prebiotics, bacteriocins and phage. Public domain investment in pre-commercial tools and technologies is needed to help progress this field.



Image: Dr David Cook, Seres Therapeutics.

The bovine ruminal microbiome: structure and function

Professor John Wallace of the University of Aberdeen discussed how modifications of the bovine ruminal microbiome could reduce greenhouse gas emissions for sustainable agriculture and lead to improvements in the quality of meat and milk.



Image: Professor John Wallace, University of Aberdeen.

The ruminal microbiome is essentially universal across species and geography, dominated by bacteria (which perform the majority of digestive processes), protozoa, anaerobic fungi, and methanogenic archaea.

Feed efficiency

In feed efficient animals (high weight gain to feed consumed), a reduction in bacterial diversity and gene richness is seen within the rumen. It is not yet understood why lower diversities are observed with higher efficiencies, however, the presence of the *Megasphaera elsdenii* in these animals aids the metabolism of lactate to propionate via the acrylate pathway. This is proposed to lower the pH to an acidity not favoured by rumen bacteria, reducing the number of species.

Fatty acid biohydrogenation

Fatty acids in cow's milk and meat are generally considered bad for human health, and are saturated through biohydrogenation by *Butyrivibrio* species. Although these species represent a tiny proportion of the phylogenetic tree in microbiomes, breeding for less *Butyrivibrio* could engineer the desired microbiome to reduce the levels of saturated fatty acids.

Methane

Ruminants are responsible for 4% of greenhouse gas production, the same contribution as the airline industry. The Extreme 8 experiment (Scotland's Rural College) looked at the four highest and four lowest methane producers in the microbiomes of 72 cattle species. Cattle microbiomes with a greater proportion of the bacterium *Succinivibrionaceae*, and those with fewer hydrogen-producing archaea species, produced less methane.

The *RuminOmics* project investigates the interplay of emissions, animal genetics and the ruminal microbiome. As the microbiome produces and regulates greenhouse gas emissions, differences in emissions must be due to differences in the microbiome, controlled in turn by differences in host genetics. RuminOmics observed a heritable core microbiome of 43 species that could be selected for via breeding. A core set of genes explained 88% of the variation in methane emissions, with a cluster of genes correlating to methanogenesis. It is hoped that identifying the genes involved could be used as a basis for selection in a breeding programme for low emission animals.

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"Remarkably, the ruminant microbiome is almost universal, with core species controlling function."

Professor John Wallace, University of Aberdeen

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Increasing agricultural productivity: the continuum of breeding, biotech and microbial products

Dr Ray Riley of Indigo Agriculture discussed the commercial application of microbial products in farming.

Throughout the last century the science, tools and underlying knowledge leveraged to improve agricultural productivity have continued evolving, leading to great improvements particularly in developing countries. Meanwhile, developments in molecular biology over the past 50 years have ushered in GM crops and their widespread use across agricultural production.

However, maintaining performance requires continuing development and applications of new technology and investment. The impact of earlier agricultural technologies (ie, synthetic fertilisers) has plateaued, and future developments in automation, agronomy and land development will require a systems biology approach that integrates metadata about the host plant and its environment, and the microbiome.

Can microbial products drive the next wave of agricultural crop innovations?

Beneficial microbes can be used to coat seeds to improve crop yield and stress tolerance, producing a plant that can resist stresses from climate changes, nutrient shortage and disease either by direct interaction with the microbe or by triggering the plant's response to stress.

Plant endophyte communities differ greatly between healthy and stressed plants with the same genotype and seed source grown in the same environment. Fingerprints of the microbiome of healthy plants can be harnessed to select microbes that can, when added to seeds, create desired outcomes. Examples identified include *Streptomyces* strains that differentially alter plant growth response and yield under drought, and bacterial endophytes that improve corn seedling vigour under different stress conditions.

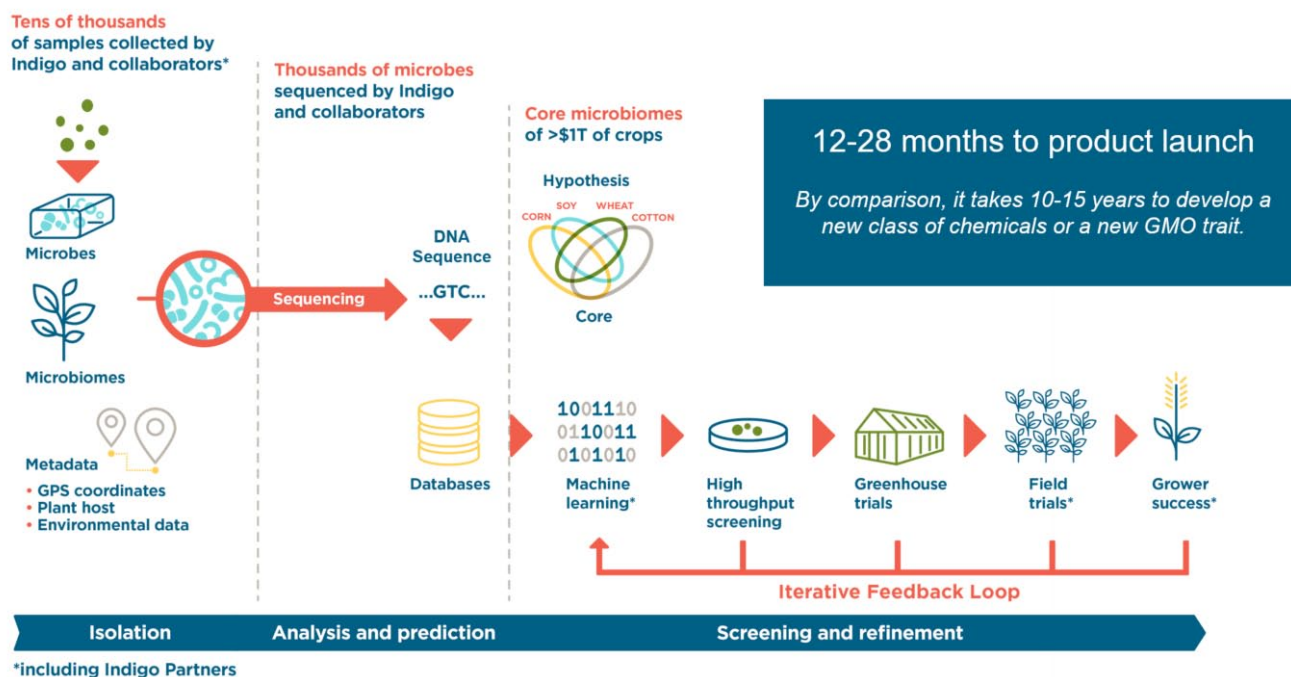
The economics of microbial treatments are very favourable. However, treatment can be sensitive to dose, formulation, and production method. It is critical to optimise stability and effectiveness of microbial treatments. Despite the many variables involved, trials spanning diverse and targeted environmental conditions can provide insightful and reproducible results. By combining technologies like machine learning and DNA sequencing, research and development of microbiome products can be achieved in as little as 12 – 28 months – significantly faster than developing a new class of crop genetics and traits or safe chemical products (10 – 15 years).



Image: Dr Ray Riley, Indigo Agriculture.

Microbiome product research and development.

Increase Farm Yields: Companion Technologies Accelerate R&D



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Progress in the field is expected through new initiatives, as agriculture becomes more consumer focused and:

- Society and government seek a more environmentally sustainable agriculture.
- Consumers push for quality and food safety.
- New technologies enable new farm management practices, like microbiology and data sciences.
- Farmers become more willing to experiment because current profit margins are not sustainable.

The plant microbiome has potential to unlock significant gains in crop yields and increase agricultural sustainability. Understanding the complex interactions between plants and the microbiome will be essential to fully realise this potential.

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“We are on the cusp of a third agricultural revolution: the plant microbiome has potential to unlock significant gains in crop yields and increase agricultural sustainability.”

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Dr Ray Riley, Indigo Agriculture

Microbiomes for improving crop production

Professor Penny Hirsch of Rothamsted Research discussed how recent advances in DNA sequencing technology and bioinformatics have improved our familiarity with soil and plant microbiomes, the complex relationships between them, and their application to sustainable agriculture.



Image: Professor Penny Hirsch, Rothamsted Research.

Soil components are structurally complex and heterogeneous, with greater diversity than any other microbiome: at least a million species in every gram of soil contribute to soil stability, terrestrial nutrient cycling, and resilience against changing environmental stresses.

Previously unculturable soil eukaryotes and prokaryotes are now being unveiled by shotgun metagenomics, advancing our understanding of the soil microbiome and revealing the effect of soil management on bacterial communities. While grassland has a higher bacterial richness than bare fallow soil, most genera are common to arable, fallow, and grassland soils despite having undergone very different treatment. Surprisingly little fungal DNA is found in agricultural soil, even in grassland; the dominant microbe type and majority of activity is bacterial.

Exploiting beneficial microbes for sustainable agriculture

Beneficial microorganisms have been exploited in agriculture since the first rhizobium inoculants in the late 19th century. Not all microbes are beneficial, but the soil microbiome is reported to inhibit pests and pathogens, modulate plant growth and improve nutrient acquisition. Many microbes known to be beneficial cannot be applied in the field without a protected niche where they can flourish, particularly for less robust surface colonisers.

With global pressure to increase food production whilst minimising fertiliser and agrochemical use, a better understanding of how to maximise the benefits of the plant microbiome, for example for nitrogen fixation, becomes increasingly important.

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“Recognising the microbiome has led to a renaissance in plant science.”

Professor Penny Hirsch, Rothamsted Research
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Exploitation of beneficial microbes for agriculture.

Exploiting beneficial microbes

Biopesticides

Bacillus thuringiensis
spray kills foliar insect
pests

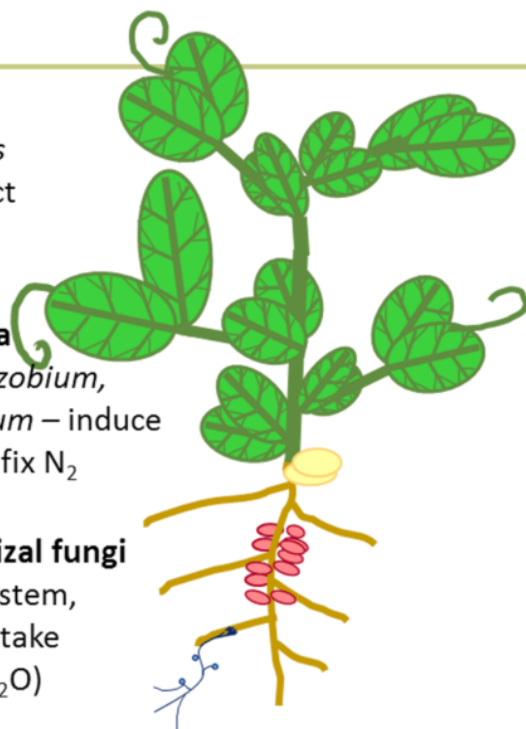
Root nodule bacteria

Rhizobium, *Bradyrhizobium*,
Ensifer / Sinorhizobium – induce
& inhabit nodules, fix N₂

Arbuscular mycorrhizal fungi

extend root system,
enhance nutrient uptake
(P, other minerals, H₂O)

Endophytic fungus *Piriformosa indica* increases salt
& drought tolerance, disease & stress resistance



Leaf & shoot colonisers

Bacillus, *Burkholderia*, *Erwinia*,
Pseudomonas - inhibit fungal
pathogens, prevent ice damage

Root colonisers

Azospirillum, *Bacillus*, *Burkholderia*,
Pseudomonas, *Agrobacterium* -
promote root growth, inhibit
pathogens

Biocontrol fungi

inhibit pathogens, infect insect &
nematode pests above and
underground

AgBiome: harvesting the plant microbiome

Dr Tracy Raines of AgBiome discussed how harnessing the microbiome can create new agricultural applications.

The agriculture industry faces mounting pressures: a burgeoning population growing to an estimated 9 billion by 2050, against fixed land and water resources. This is further challenged by a 30% yield loss to pest, disease, and nematode pressures, despite excellent agronomy and chemical solutions.

AgBiome seeks to harness the solutions that plants use to protect themselves in nature and has gathered over 7,000 environmental samples to populate their Genesis™ database. Whole genome sequences are essential for accurate microbial discovery: 16S sequencing alone cannot be relied on to provide details about strains or strain activity. AgBiome's searchable database tracks every microbe in the collection including metadata and contains over 200 million genes and almost 49,000 whole genome sequences. This approach is based on the idea that the larger the collection the better the strain and product.

Genesis™ allows AgBiome to capture and screen plant-associated microbes to identify agriculturally relevant applications, narrowing down from trillions of microbes to thousands of strains and hundreds of biological leads, or from millions of gene sequences to thousands of trait candidates.

Environmental samples are fractionated by plant compartment so that they can be applied more readily in that setting (eg endophytic compartments of roots). AgBiome's screening platform allows for faster and smarter selection of candidate microbes. The first microbe screened through the assay is unlikely to be the most active. Given the valuable data that is collected upfront, once an active strain has been found, the most related strains are prioritised for testing through the same assay to uncover the most attractive biological lead faster.

Looking to the future

- AgBiome aims to continue sampling in the US and countries beyond to increase the number and diversity of microbes in the database. Biological product discovery has about a 1% success rate and requires years of random screening: the best way to find a successful product is to continue sampling and growing the collection.
- They aim to produce plant trait products as well as microbial products: they have discovered thousands of genes with insecticidal properties.
- AgBiome has many CRISPR elements in their database, including yet uncharacterised unique and novel editing elements which could create new intellectual property.



Image: Dr Tracy Raines, AgBiome.

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"It really is an arms race out there in the soil: we see resistance problems around every ten years."

Dr Tracy Raines, AgBiome
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Dissecting the role of multi-kingdom microbial consortia on plant health

Dr Stéphane Hacquard of the Max Plank Institute for Plant Breeding Research discussed the impact of the bacterial root microbiota on fungal and oomycetal community structure and diversity.

Bacterial microbiota are essential for plant survival and protection against root-derived filamentous eukaryotes, while biocontrol activity of bacterial root commensals is a redundant trait that maintains microbial inter-kingdom balance for plant health.

Microbiomes and plant health

Plants roots are colonised by diverse bacteria with functions including nutrient acquisition, immunomodulation, and pathogen protection. To benefit agriculture, the consequences of plant microbiota on plant health need to be elucidated further.

The major physiological function of the bacterial root microbiota is to protect plant roots from root-associated fungi and filamentous eukaryotes. Inter-kingdom microbe-microbe interactions help establish the microbial community along the soil-root continuum, and interactions that combine fungi, bacteria and oomycetes significantly promote plant health when compared to microbe-free plants.

Perturbations in filamentous eukaryotes cause shifts in fungal and oomycetal communities, while the bacterial community remains stable. These bacteria-mediated community shifts promote plant growth. Bacterial root microbiota suppress fungal growth, with similar inhibitory activities exhibited by most strains. The bacteria *Comamonadaceae* and *Pseudomonadaceae* are relevant for plant growth rescue in the presence of fungal communities, and could be used in agriculture to protect from fungal pathogens.

Microbiomes for agricultural improvement

Establishing better microbiomes for agricultural improvement falls into two categories: pest or pathogen management and yield improvement. Recent studies suggest that monoculture, pesticides, and fertilisation may have altered the symbiotic efficiency between plants and microbes. Meanwhile, microbiota-mediated beneficial traits on plant health are likely to be counter-selected in agricultural systems.

There is a need to restore microbial diversity, moving from high-input low diversity agriculture to low-input, high-diversity. One way is to establish microbial inputs and synthetic microbial communities from wild crop varieties, restoring indigenous plant microbiota. This could be done by direct inoculation of synthetic microbial communities in the field using a single strain or low-diversity synthetic community, or complex microbial inoculants with high taxonomic diversity. This must ensure invasion and persistence of microbiota in the field, without disturbing indigenous communities.



Image: Dr Stéphane Hacquard, Max Plank Institute for Plant Breeding Research.

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“The bacterial community in plant roots is much more diverse than in animal guts, because soil is one of the richest microbial inputs on Earth.”

Dr Stéphane Hacquard, Max Plank Institute for Plant Breeding Research

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A soil-borne legacy: disease-induced assemblage of a plant-beneficial bacterial consortium

Dr Roeland Berendsen, Utrecht University, discussed how diseased plants adjust their root microbiome upon pathogen infection and recruit a group of disease resistance-inducing and growth-promoting beneficial microbes.

Disease suppressive soils exist in nature for many plant species and pathogens. These soils typically develop after a disease outbreak due to the subsequent assembly of protective microbiota in the rhizosphere. This enhances protection against the pathogen in a second population of plants growing in the same soil, maximising the chance of offspring survival.

The rhizosphere microbiome can modulate plant immunity to induce systemic resistance or increase susceptibility to plant pathogens. For example, *Pseudomonas simiae* WCS417 affects the microbial community, priming the immune system to respond faster and more strongly to invading pathogens, fungi, bacteria and insects.

'Cry for Help' hypothesis

The 'Cry for Help' hypothesis states that when plants are under biotic or abiotic stress, hormonal defence signalling recruits beneficial microbes that help defend against the attacker. Upon above ground infection of *Arabidopsis* plants the following is observed:

There is specific promotion of a consortium of three bacteria. The promoted strains are beneficial for plant health, inducing resistance and promoting growth, with synergy among promoted strains. Although separately the three bacteria do not significantly affect the plant, together they induce systemic resistance and promote growth. Recruitment of beneficial microbes benefits a next generation of plants. Soil that is preconditioned by infected plants shows more resistance than soils preconditioned by healthy plants, indicating a soilborne legacy that protects the next generation.

Infected plants have a distinct root exudate profile. A defence-related hormone signature, as observed during pathogen and insect attack of foliar tissues, may influence the composition of root exudates and therefore the composition of the rhizosphere microbiome, indirectly

inducing resistance. These exudates could have an application as a prebiotic to create better microbiomes.

Future opportunities

Future opportunities to apply knowledge of the microbiome to agriculture include creation of modular microbiomes that protect plants against stress, personalised plant medicine, and microbiome-optimised plants.



Image: Dr Roeland Berendsen, Utrecht University.

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“The root is the gut inside out: they are the main organs for uptake of nutrients and water, and contain beneficial microbiomes that assist in nutrient uptake, prevent pathogen colonisation, and modulate host immunity.”

Dr Roeland Berendsen, Utrecht University

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Panel session: challenges, needs and opportunities over the next decade

The meeting ended with a panel discussion investigating common themes across use of microbiomes in agriculture and medicine, future opportunities, challenges, and the actions needed to deliver an exciting future. Chaired by Dr Mike Romanos of Microbiotica, the panellists were Professor Ian Charles, Quadram Institute; Dr David Cook, Seres Therapeutics; Professor Penny Hirsch, Rothamsted Research; Professor Denise Kelly, Seventure Partners; and Dr Ray Riley, Indigo Agriculture.



Image: Conference attendees.

Opportunities and the shape of the industry in 5 – 10 years

- There is societal awareness and acceptance of microbiome science due to its harnessing of natural microbes, and some consumer appetite to commercialise useful aspects. However, despite public interest, large companies are risk averse, especially for new modalities such as products based on live bacteria, until there is proof of concept.
- Over the next five years, successful trials and licenced products will change perception of the microbiome such that larger pharmaceutical or agribio companies will collaborate with biotech, providing the resources to bring products to market.
- In five years many microbiome-based medicines will be completing Phase 1 trials, with several more at Phase 3 and one or two licensed products launched. The next decade will provide key learnings in how to translate microbiomes, creating a foundation for further growth in the sectors with a step change towards becoming a mature field of biomedicine and new product modality.

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“The microbiome is a real opportunity for a person in plant breeding to create tools to add value, address problems, and increase productivity.”

Dr Ray Riley, Indigo Agriculture

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- Use of the microbiome as a biomarker to stratify disease and predict patient response to therapy could be a profound development within the next decade. Clinical proof of concept will act as a catalyst for productivity and development across all therapeutic modalities including existing conventional ones.
- While immunotherapy and metabolic applications are of great near-term potential, the gut-brain axis represents a particularly exciting emerging area of new biology linking the immune system, nervous system, and gut microbiota to address major unmet medical needs.
- The UK agricultural industry could be significantly different in 5 – 10 years with many microbiome-based agricultural products coming into the market, but only with major changes in strategy and policy. Progress is underway elsewhere, and some of the first products are in commercial agriculture already in the US.
- There is the opportunity for the UK plant breeding and crop genetics communities to adopt microbiome-plant interactions as a new trait or series of traits and ensure that our crop varieties are optimised for interactions with soil and endophytic microbiomes.
- Many new technologies will be required to feed a population of 8 billion, including new tools in microbiome and plant genetics based on understanding of gene functionality, legacy genetics, and plant interactions with microbiomes.
- Soil and plant microbiomes could be used for more productive, sustainable, and lower input agriculture, for example by reducing or replacing chemical pesticides herbicides and fertilisers. It is predicted that current crops will be integrated with older varieties that need lower levels of nitrogen fertiliser and gain nitrogen more efficiently from soils, providing that optimal microbiomes are exploited.

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“The microbiome is like finding a whole new planet in the Solar System – and it’s got life on it. This is a whole new organ for drug discovery, to visualise, and to explore for its impact on human health.”

Professor Ian Charles, Quadram Institute

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Obstacles to translation and economic factors

- Due to the scale and complexity of the biological data, there is a need for multidisciplinary and cross-sector collaboration (academia, biotech, large companies) and resource sharing (culture collections, datasets and computational tools) to deliver scientific understanding and successful translation.
- There is a need to reduce the cost and computational requirements of large-scale genomic sequencing and clinical trials for both academic institutions and biotech companies.
- There are significant skills gaps in the UK in a key areas including microbiology and data science. It is challenging for companies to recruit informaticians, already in short supply, in direct competition with tech giants and other sectors.
- There is a need for in-house training of fermentation scientists and chemical engineers to solve the unique manufacturing challenges associated with live bacterial and fungal products.
- In the agriculture sector in particular there are problems associated with the storage of live microbiota over the time periods and in the environments associated with farming and crop production.
- Public responses to the application of live bacteria and fungi to crop plants and soils remain to be tested, especially in Europe, where sensitivities to interventions in environments and food sources remain high and have major effects on policy.



Image: The panel members, from left to right: Professor Penny Hirsch, Professor Denise Kelly, Dr David Cook, Dr Ray Riley, Professor Ian Charles, Dr Mike Romanos.

Policy

- The microbiome represents a new branch of biology both in medicine and agriculture, and the start of a new commercial sector in the life sciences with great opportunities. However, there is insufficient basic research investment by the public and charity sectors in the UK to compete in the field, accelerate research translation and train sufficient scientists with the required skillsets.
- There are therefore few UK start-ups in this field compared to the US or continental Europe, and UK biotech companies struggle to attract experts compared to those in the US and other EU countries. Changes in policy could help the UK become a leader.
- As few young UK scientists go into bacteriology or microbiome research, much recruitment is from continental Europe and this has become more challenging recently. The UK's ability to bring in top class, well trained people from overseas will influence its ability to compete in microbiome research and its translation.
- The biomedical regulatory field is rapidly evolving and currently regulators are receptive to biotech companies taking live bacterial products into clinical trials as they see the potential benefits regarding safety and functionality in areas of unmet need.
- The agricultural regulatory field is evolving rapidly in the US but lags behind in Europe, where consumer reactions and the precautionary principle undermine rapid formulation and adoption of guidelines and legislation.
- In agriculture, work on microbiomes is more readily translated because proof of concept can be carried out in the target organism, rather than requiring testing in model organisms and translation into human studies, with the usual attrition rate that this brings. Nevertheless, there needs to be leadership within the UK to stimulate early adoption to make the UK an attractive place to implement the technologies and new sustainable agriculture.

Conclusions

Microbiomes in the human gut, rumen of farm animals, soils and crops are essential for life. This has always been the case because advanced forms of life have always exploited the prior existence of the microbial world, so seeking to exploit microbiomes for the betterment of human life and agriculture is nothing new. New opportunities arise because we have recognised the potential of optimising and using constituents of microbiomes to enhance quality of life, food production and the environment. While the conference confirmed the potential for extraordinary advances, we learnt that the UK is not currently a clear leader. With vision and commitment to drive production of more knowledge, stimulate translation and create the policy support required to bring such innovations into daily life, the UK could become such a leader.

Acknowledgements

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