Innovation Networks | Microbiome

Microbiome Strategic Roadmap

This report reviews the landscape of microbiome science and innovation within the UK. In line with the “one health” approach, it spans human, animal and plant sectors with key recommendations on how to advance science translation and business creation.

Contents

Please note: Regarding the Forward and Summary, in our capacity as editors of this report, we have endeavored to capture accurately the key elements and recommendations of the individual chapters that follow. However, the authors of the main chapters are not responsible for the content of the Foreword and Summary sections including any possible errors.

Foreword

The KTN Microbiome Innovation Network or "KTN MIN" (formerly known as a Special Interest Group), was launched at the end of 2019 with the following vision, mission and goals:

VISION: *UK to be recognised as a world leader in microbiome research and innovation.*

MISSION: *To develop a proactive, self-sustaining microbiome community in the UK to raise the visibility of the UK's world leading microbiome science and enable translation of this science to the benefit of the academic institutions, start-ups, SMEs, larger established companies that operate in the UK, and to society at large.*

GOALS: *include: raising visibility of, access to and investment in UK microbiome science and innovation and fostering an environment that supports the creation of new start-ups, scale-up transitions, industry partnerships and impact on jobs and GDP.*

With these objectives in mind, the KTN MIN Advisory Board decided to embark on the development of a microbiome landscape map and a strategic roadmapping exercise with this report representing the product of the latter.

The relationship between microbes, their hosts and the environment is the subject of intensive research as it holds the promise of providing vital solutions for some of society's biggest challenges including chronic and infectious human diseases, consumer health and wellbeing, plant and animal agricultural productivity and the ongoing threats of antimicrobial resistance and pandemics. Catalysed by the genomics and systems biology investments made over the past two decades, this new interdisciplinary field has come to be known as "microbiome science" and has been made possible by an assembly of capabilities spanning biology, analytical chemistry, computer science and statistics and a life sciences infrastructure that enables deep discovery to large scale trials and everything in between. Globally, there has been significant investment in the field especially from venture capital and global science-based companies resulting in the emergence of many new start-ups especially pharma biotechs, some of which are in late-stage clinical trials with their candidate products.

As this report reveals, the UK has a world-leading position in the science of the microbiome especially as it relates to human health and wellness but also a strong position within the animal and plant-based agriculture sectors, too. Moreover, the UK also has some of the world's leading pharmaceutical, consumer health and wellness and agritech companies, a biotech ecosystem that is one of the most successful in the world, a supportive environment for life sciences and biotech start-ups and scale-ups and a constructive regulatory environment.

Despite these advantages, compared to North America and some other European countries, the UK has, with a few notable exceptions, seemingly not been so successful in translating its leading edge microbiome science into business creation. There are various explanations but also opportunities to overcome this especially if the UK builds on its strengths in the life sciences and identifies the opportunity spaces where it has the basis to establish a differentiated and world-leading position in microbiome science translation. This is the subject of this strategic roadmap report.

In line with the One Health approach, this report covers human, animal and plant sectors as well as cross-cutting aspects including enabling technologies, biobanking, manufacturing, diagnostics, intellectual property and regulatory dimensions. It is based on a pre-competitive analysis of this rapidly evolving field by a group of 74 leading industrial and academic scientists and includes recommendations for pre-competitive priority actions necessary both to ensure the UK is able to maintain its leading edge microbiome science as well as to translate this into business creation and economic growth.

Each section of the report is written by an expert team drawn from industry and academia from within the UK and, whilst each section has been intentionally compiled to be read as a stand-alone chapter, the recommendations made in each of these sections lead to common themes and priorities as well as selected sector-specific priority actions that have been brought together in the Summary section.

Dr. Andrew Morgan, Chair of the KTN Microbiome Innovation Network

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Summary and Recommended Precompetitive Priority Actions

1 **Foster a "Microbiome Centres of Excellence" Approach:** UK institutions with significant activity in the field of the microbiome should be encouraged to make themselves more visible and accessible to potential collaboration and investment partners from within the UK and internationally. This does not necessarily involve significant additional investment as the simple step of promoting an institution's collective capabilities and activities in microbiome science research and providing a means to connect those external to such institutions could have a meaningful impact. For example, the University of Oxford's Kennedy Institute recently established the Oxford Centre for Microbiome Studies to make its capabilities known and accessible. As one contribution towards addressing this recommendation, the KTN Microbiome Innovation Network has already taken steps to create an online landscape map thereby providing a portal to UK microbiome research and innovation.

2 **Create Microbiome Research & Innovation Collaboration Networks / Virtual Microbiome Institutes:** One of the observations made in the analysis is that the UK has high quality microbiome research spread across many disciplines and institutions. This is not in itself a bad thing but it does mean that we have to take steps to ensure the research is not conducted in silos and that the investments being made by the research councils and other funding bodies can be aggregated through strategic investment in the establishment of microbiome research collaboration networks that bring together and develop the various skills and knowledge required collaboratively and at a scale needed to increase the impact of UK microbiome science significantly and ensure UK competitiveness in this rapidly emerging field of science. It is envisaged that these networks would have the potential to function as or develop into "virtual microbiome institutes".
Whilst the core of these networks would most likely be assembled around consortia of universities and institutes, it is important that industry, knowledge transfer, venture capital, standards, regulatory and IP and other expertise needed for translational research and innovation also participate in an integral way in order to foster closer links between academia, industry and healthcare and to maximise the opportunity for R&D collaboration, funding, innovation and business creation. By way of example, the MRC Partnership Scheme can provide a mechanism for the creation of a consortium of universities and institutes needed to scale research in the field of human health and wellbeing and this can then be added to through the participation of those with the expertise needed for translation and innovation including the NHS perhaps with Innovate UK and KTN support.

We envisage the creation of the following microbiome research and innovation collaboration networks:

- A human microbiome research and innovation collaboration network.
- An animal microbiome research and innovation collaboration network.
- A plant microbiome research and innovation collaboration network.
- A standards network for establishing microbiome research and biobanking standards.

It is envisaged that these new networks would remain affiliated to and connected with the KTN MIN (or a UKRI successor) thereby enabling connectivity across the above sector and subject-specific networks. In effect, a microbiome network of networks or web is proposed connecting both nationally and internationally. Moreover, the KTN MIN teams of academic and industry scientists and others who have contributed to this strategic roadmapping report are well-placed to assist in the initiation, assembly and implementation of the new network of networks.

3 **Encourage Microbiome Entrepreneurship, Seed Funding, Regulatory and Intellectual Property Rights Support:** There is an urgent need to create an environment that leads to more translational opportunity, such as more spin-outs and start-up companies and industry-academia collaborations and strategic partnerships. To achieve this, it is important to mobilise microbiome seed funding and advisory support from sources such as UKI2S to support microbiome entrepreneurship for pre-start-up proof of concept work and early stage start-up funding. It is critical that academic researchers and early-stage entrepreneurs are made aware of these opportunities and are assisted by national and local advisory and networking support organisations to transition good ideas from the laboratory to business concepts and the creation of new enterprises.

One proven way to bring business and funding support closer to the research is through the creation of incubator hubs alongside selected microbiome centres of excellence.

Beyond business skills and funding, understanding the importance of a regulatory and an IPR strategy to value creation and developing a sustainable business is challenging and the field of microbiome is especially complex. Therefore, ways to support start-ups and other SMEs navigate this dimension is vitally important through the provision of adequate regulatory and IPR training.

The KTN MIN is one of the bodies that can assist in connecting seed funds and start-up advice to the UK microbiome research and innovation community, whether for seed funding, IPR training, or for accessing regulatory and technological support.

4 **Ensure Support for and Access to Emerging Enabling Technologies:** We are increasingly seeing the uptake and value of long read sequencing, with single cell sequencing also beginning to come online. The application of these technologies will significantly aid the generation of single-amplified and metagenome-assembled genome libraries and contribute to our understanding of the physiology of the collective microorganisms being studied. The ongoing roll out of portable sequencing, meanwhile, offers game-changing potential to truly democratise the technology, opening new possibilities for precision tailored medicine, nutrition, agritech, and so on, based on personalised or localised microbiome analysis.

At the same time, construction of a more complete understanding of the systems under investigation requires that we move beyond measurement of microbial DNA. Here, technologies like microfluidics and mass spectrometry come to the fore, enabling techniques such as metabolomics to provide mechanisms to model communications between microbes and their hosts and thereby provide a more functional perspective. The availability of these data and their integration with sequencing data, is needed in order to realise the potential of microbiome diagnostics and to discover new microbiome therapeutic modalities including small molecules.

The UK needs to maintain its strong position in microbiome science-enabling technologies. The microbiome networks construct proposed here should enable the microbiome research community to collaborate in such a way as to effectively share access to the advanced analytical equipment and capability and the emerging new technologies needed and thereby accelerate advances in both research and innovation in this field.

5 **Establish Microbiome Research Standards:** As mentioned above, it is recommended that a microbiome research and innovation collaboration network is set-up specifically for the development of standards in microbiome research and biobanking. At present, there are no international standards specifically for microbiome research and this can reduce the confidence in data and impact on its downstream use. Variability exists across sample collection, sample analysis, and results reporting. Access to high-quality datasets, including metadata, commutable across laboratories is needed for meaningful interpretation of results. Establishment and curation of comprehensive databases is an important aspect of standardisation, too. Standardised reporting of results is fundamental to integrating microbiome science into the clinical arena in order to ensure consistency for patients and practicality and easy comprehension for clinicians. Standardisation is equally important for human clinical diagnostics and biobanking as it is for microbiome research across the animal and plant sectors where there are needs to meet environmental and legislative standards. Recognising that facilitating standards uptake and adherence is also a challenge, development of mobile apps and IoT technologies, such as wearables, could potentially play a role here, through capturing and structuring appropriate data.

6 **Develop "Next Generation" Biobanking:** Biobanks and culture collections are essential and integral to storing and distributing biological materials for research and innovation in human health, nutrition and wellbeing as well as for animal husbandry and plant agriculture. They are repositories of archival tissue, preservers of genetic diversity, providers of microbes for biomanufacturing and for the production of live biotherapeutics, probiotics and potentially other microbiome modulating modalities.

Many organisms cannot be cultured in isolation because of some dependency on another organism, metabolite or culture condition. Using high-throughput research infrastructure to dramatically increase the number of strains that can be isolated and grown is essential. Leveraging existing investment in UK high-throughput infrastructure, and understanding the requirements of the microbiome community to advance biobanking technology should offer significant return to the UK bioeconomy through the isolation and characterisation of biotherapeutic, agricultural and soil health and consumer products.

In addition to establishing standards for microbiome biobanking, the proposed standards network for microbiome research and biobanking should be chartered to support and facilitate the development of "next generation" biobanking for human, animal and plant microbiomes research and innovation building on the UK Crop CryoBank microbiome project and the advances being made in developing a human gut bacterial culture and genome collection at the Wellcome Sanger Institute.

7 **Harness the Potential for New and Rapid Diagnostics:** Whilst microbiome diagnostics has potential in plant, animal and human health and disease prevention and treatment, it is in the field of human health where we see the most progress. Studies have linked the microbiome to disease onset, progression, and therapy response across a range of areas, particularly chronic autoimmune and inflammatory conditions for which cures are not yet available, but also including obesity, cardiovascular disease, and cancer. As such, there is a vast scope for where microbiome diagnostics could be used in the clinic. A number of specific applications are envisaged that would bring substantial health economic benefits, making microbiome diagnostics an important tool in the future of precision medicine.

Given its leading microbiome science and a national health system that allows for the development and integration of datasets from large long-term cohort studies, the UK is in a unique position to develop microbiome diagnostics. Despite this excellence and the emergence of several start-up companies working in the microbiome diagnostics space, the UK needs to do much more to identify and translate the promise of microbiome diagnostics into clinical reality and to leverage this capability for the benefit of animal and plant sectors, too.

Key to success here, again, is the implementation of the wider recommendations in this strategic roadmap including upscaling and integration of capabilities and programmes by drawing together academia, industry and healthcare through a microbiome research and innovation collaboration network of networks and a funding regime that is more microbiome-centric rather than focussed on diseases where the microbiome is implicated.

8 **Invest in Microbiome Process Development and Pilot-Scale Manufacturing:** Due to the current worldwide focus on high value manufacturing for cell and gene therapies, there is a massive shortage in global capacity available for fermentation and finished dose manufacturing with the flexibility and expertise to fully exploit the potential benefits of microbial based therapeutics. In order to address this serious bottleneck in microbiome product development, support is needed for process development scale-up and small batch manufacture (fermentation and finished dose) to provide academics and start-ups with material for pre-clinical and clinical development, coupled with commercial manufacture capability to support the pipeline of products entering later stage clinical trials. Possibilities to be explored range from building these capabilities with an SME or with CPI (Centre for Process Innovation) or Porton Down to creating a fully dedicated new centre for this.

9 **Promote a Supportive Regulatory Environment:** The UK is highly recognised worldwide for its well-established regulatory framework and practices, which are so vital for enabling innovation in the life sciences. Ensuring regulations, rules and good regulatory practices encourages advances that target unmet needs, mitigate any unintended consequences of the developments and are based on good regulatory principles is paramount to help secure the economic and societal benefits of world-class microbiome research across the UK.

There is evidence that the fast pace of microbiome developments clearly challenges existing regulatory frameworks as the development of microbiome solutions may be novel or produced by an entirely novel approach and may not even fit easily into existing well-established regulatory routes, which can make the whole process of regulatory approval challenging.

Several approaches to regulation could support microbiome innovation. For instance, single points of access for early and close dialogue between developers and regulators, exemplified in the therapeutic area by the MHRA Innovation office, would ensure that pitfalls are avoided by providing easy access to regulatory advice and requirements. While scientific guidance is being developed by interested stakeholders, further development and elaboration of standards and regulatory guidances that outline and clarify specific requirements would also greatly aid navigation of the regulatory frameworks for developers.

Innovation systems, such as the microbiome network of networks proposed here, that enable interaction and information exchange between the actors in the system, are known to drive the innovative performance of industry including future rule making development. It is vital that we bring regulation and standards close to the research and development and, in order to achieve this, it is proposed that experienced regulatory experts should be integral members of the microbiome network of networks and of the proposed standards network for establishing microbiome research and biobanking standards in particular.

10 **Improve Microbiome Education, Skills and Talent Pipeline:** Firstly, it is important to address the challenge that microbiology, which is at the core of microbiome science, is today only a small and somewhat forgotten component of most biological degree courses despite the UK having had a long and successful tradition in the field of microbiology. The proposed microbiome research and innovation collaboration networks should be chartered to help rectify this situation through educational outreach and involvement in the development of course curricula including courses in microbiome science.

Furthermore, few researchers possess expertise in the full data continuum, from data generation to multi-modal analysis, and this can lead to suboptimal experimental design. Researchers may find themselves unable to access the requisite tools and techniques because of the gulf between the biological and computer science fields that represent either ends of the data continuum. The knowledge gap between biologists, computer scientists and statisticians will increasingly become an issue as multi-modal analyses come on stream, with multiple disparate networks of data to integrate and interrogate. To address this, cross-disciplinary training is required to maximise knowledge exchange between disciplines, catalyse experimental co-design, and enable researchers to access emerging technologies that are germane to the field. Recognising the interdisciplinary nature of the challenge, the microbiome research and innovation collaboration networks proposed here ("virtual institutes") could create the foundation for the provision of this necessary training.

The microbiome network of networks would be well placed to assist in public engagement using evidence-based science to ensure that knowledge of the microbiome, its current limitations and its potential is widely and accurately understood by patients and consumers and by medical, animal and plant professionals. The British Society of Gastroenterology and Guts UK are leading the way in this educational outreach but substantially more support is needed.

11 **Prioritise support for specific opportunities where the UK has a distinct advantage:** This report identifies some specific precompetitive priority areas where the UK has or has the potential to develop a distinct advantage and where there is opportunity space for the UK to establish a leading position in the underpinning science and in business creation. Several precompetitive priority support areas have been identified:

Human health, nutrition and wellness

a. Intestinal Microbiome Transfer (IMT – aka FMT) and Intestinal Microbiome Medicinal Products (IMMP): In the US, several start-ups have now progressed to late-stage clinical trials demonstrating the safety and efficacy of IMT/IMMP for treatment of recurrent *C. difficile* infection and market approval is expected in 2020-21. This has provided a significant boost to the field of microbiome therapeutics as IMT and IMMP drug development has paved the way for the new field and can play an important role in the discovery of Live Biotherapeutic Products (LBP) and other Therapeutic Modalities. The UK's unparalled enabling infrastructure for IMT (formerly known as Faecal Microbiota Transplantation or FMT) positions the country to become a leader in translational IMT research and a highly competitive hub for IMMP drug development and commercialisation.

b. Live Biotherapeutic Products and Other Therapeutic Modalities: LBPs are being developed either as single bacterial strains or as multi-strain consortia. LBP discovery is driven by bottom-up (strain screening for functional properties), top-down (microbiome compositional signatures correlating with a positive patient response) and ecology approaches and is the key focus for many microbiome therapeutic start-ups around the world.

One of the main challenges, however, is the need to conduct the required research and clinical studies at a resolution and scale needed for the discovery and development of human therapeutics. This has proven difficult to achieve but this is where the UK has an advantage through a combination of world-leading capabilities in high resolution microbiome multi-omics analyses at scale (most notably metagenomic sequencing and metabolomics) and the ability to conduct gold standard clinical studies using robust clinical cohorts made possible through the NHS and organisations such as CRUK. This "platform" is what is required for the discovery and development of superior LBPs and other therapeutic modalities such as selected microbial metabolites and signalling molecules sometimes referred to as, "drugs from bugs", a direction that fits very well into the UK's well-established position in high throughput research infrastructure.

Choosing the right microbiome targets is also important and here the UK needs to play to its strengths and to the opportunity space that exists in neurobiology (gut microbiome-brain axis), oncology (gut microbiome/immunotherapy response and tumour microbiome), vaginal/urogenital health (a major unmet need) and respiratory diseases especially Covid-19 where the importance of the gut-lung/lung-gut axes in directing an individual's immune response to SARS-CoV2 warrants urgent attention.

The UK's world-class life sciences infrastructure includes institutions (universities and institutes) where the skills and facilities exist for conducting leading edge microbiome science. Nonetheless, for this multidisciplinary endeavour to succeed both in the science and its translation, as proposed earlier, there is a need to upscale by pooling these capabilities through the formation of collaborative consortia/partnerships across these institutions. This can be achieved by forming a human microbiome research and innovation collaboration network into which the translational and innovation skills can be added. In addition, there is a need to appropriately fund the associated programmes for translational success, see below:

c. Nutrition and Wellbeing: Diet is one of the most important and effective means of modulating the microbiome, improving health and reducing healthcare costs. In order to harness this potential, it is proposed that we need to build on the experience of the past 20 years in dietary fibres, prebiotics and probiotics in the consumer health arena, and conduct the large-scale, robustly designed, multi-centre clinical trials needed to demonstrate clearly the health benefits of these and emerging microbiome modulating nutritional interventions as well as to address the current regulatory limitations. Proposed priority areas for the UK are immunomodulation, gastrointestinal health and emerging areas such as gut-brain axis, metabolic health, healthy ageing, women's health and the gut-skin axis.

d. Personal Care and Hygiene: This is an important sector for the UK economy with some of the world's leading PC&H companies being based here and, with more than 50% of the UK population suffering from a microbiome-associated skin complaint each year (thereby placing a substantial burden on the NHS), there is a clear and pressing need for solutions. Despite the importance of the PC&H microbiome research and innovation to UK export led growth, employment and the individual wellbeing of consumers, the sector has not so far been recognised in UK research strategy, science education, inward investment and small-tech sectors. This needs correcting. As with nutrition and wellbeing, clarity on the UK regulatory status of consumer product microbiome innovations is also needed to unlock research and commercial investment.

One of the key steps to enhancing microbiome science and innovation for human health, nutrition and wellness will be the establishment of a human microbiome research and innovation collaboration network.

Animal Nutrition and Health

With its significant strengths in both commercial and academic sectors, there is a clear opportunity for the UK to take a lead in the development of microbiome solutions for the companion, working, sport, leisure and production animal sectors, which, combined, are worth £27 billion annually to the UK economy. In addition to improvements in animal health, microbiome science offers significant opportunities to improve welfare, performance and environmental impact of animal production and husbandry. With a clear focus on outcomes, a framework can be built that considers the role and modulation of microbiomes in terms of productivity coupled with product quality in farmed animals together with quality of life and owner experience in companion animals. The UK can lead an evidence-based approach to the development of a dietary, husbandry and genetic approaches to the control of animal microbiomes enabling significantly decreased livestock greenhouse gas emissions contributing to the move towards Net-Zero.

An animal microbiome research and collaboration network will enable the academic-industry connections required to enhance innovation in this sector. Moreover, by including the different animal species of economic interest and through links to the other proposed microbiome networks for the other sectors, it will make it possible to leverage the wider microbiome knowledge and skills needed to advance science and innovation in the field of animal nutrition and health.

Agri-Food and Nutrition - Crop and Soil Health

With its leading edge microbiome science coupled with some of the best plant research centres in the world, the UK has the opportunity to become a world leader in the development of agricultural biologicals, the market for which is projected to reach more than USD 10 billion in 2020.

Three priority areas have been identified where the UK can succeed:

- Novel biocontrol/growth stimulation microbial products avoiding the need for chemical intervention and driving towards sustainable agriculture.
- Natural product discovery and exploitation (for healthcare, better nutrition and agrichemical replacement).
- New germplasm for soil sustainability and better advice to farmers.

These priority areas address the needs for sustainable production of food, improvement and sustainability of the environment (enhanced carbon capture, flood mitigation and natural attenuation of pollutants in soils) and increasing innovation in agritechnological products. Fundamental to success in delivering chemical free, zero carbon sustainable agriculture is an understanding of the plant/rhizosphere microbiome and its critical contribution to plant nutrition and health and soil function.

Although a number of important steps have already been taken to support the UK's potential for microbiome innovation in the agri-food and nutrition/crop and soil health sector (e.g. the investment in National Agri-Tech Centres and UK-Crop Cryobank microbiome project), the very significant opportunities for the economy, food security and the environment will require substantially more support if the potential is to be realised.

To address these opportunities further, an important first step will be to build the necessary academic-industry connections through a plant microbiome focused research and innovation collaboration network aligned to similar networks for other sectors as proposed earlier.

12 **Increase Strategic Funding for Microbiome Research and Innovation:** This report has taken a wide ranging view of the state of microbiome science and innovation in the UK and has reached clear and actionable recommendations, the most important of which is to draw academia, industry and healthcare together into collaborative networks to bring together and develop the various skills and knowledge required collaboratively and at a scale needed to increase the translation and impact of UK microbiome science significantly and ensure UK competitiveness in this rapidly emerging field of science.

Given that delivery of the recommendations outlined in this strategic roadmap cut across the scope of the different research councils, implementation would be greatly assisted if UKRI is able to adopt "microbiome" as a strategic priority and lend its support to the roll-out of the key priority actions.

In addition, "pump-priming" funding is needed for the roll-out of and day to day support for the functioning of the proposed microbiome network of networks. This will require only a modest increase in the level of funding especially as it relates to kick-starting interactions between academia, industry and healthcare. The benefits will follow in terms of helping to drive earlier and stronger engagement of academic institutions with industry and healthcare, the identification of pre-competitive priorities, the take-up of new funding opportunities, the transfer of ideas from laboratory to proof of concept as well as investment in new start-ups and collaborations by seed-funds, venture capital and industry and, as appropriate, with the support of Innovate UK, Scottish Enterprise and others.

A more significant investment and new funding model is required for the strategic funding of larger multidisciplinary programmes, skills and infrastructure targeting the priority areas outlined in this report and through institutional collaborations that combine the UK's world-leading science to achieve the scale and impact required in this highly competitive field. In particular, a more integrative model of microbiome research funding by UKRI is needed for microbiome-centric programmes, including postgraduate training and educational outreach, otherwise such programmes can fall between research councils and/or between specific funding priorities such as different disease focus areas. For instance, microbiome enabling technologies and diagnostics are clear examples of where such strategic funding is needed. Similarly, continued funding of the microbiome research infrastructure is needed to ensure the UK's strengths in the science are maintained and extended as well as funding of selected facilities such as microbiome incubators and, not least, a process development and pilot-scale manufacturing facility for live biotherapeutic products and other microbiome-based solutions.

It is not necessarily the case that significantly more additional funding will be needed overall to achieve the objectives of this proposed strategy as one of the primary benefits of upscaling the research effort through a microbiome research and innovation collaboration network of networks will be greater efficiency.

With thanks to Dr. Jethro Johnson from the Oxford Centre for Microbiome Studies for critically reading this Summary section and for providing very helpful comments

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Section 1.

Intestinal Microbiome Transfer

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Section 1. Intestinal Microbiome Transfer

Intestinal Microbiome Transfer (IMT)

Intestinal microbiome transfer (IMT), previously known as faecal microbiota transplantation (FMT), is a medical procedure that involves the transfer of microbial ecosystems derived from rigorously screened donors into the intestinal tract of a recipient with the intention of preventing or treating a disease. IMT is widely regarded as the most effective therapeutic modality for patients suffering from recurrent *C. difficile* infection (CDI), with a large body of randomised controlled clinical trials reporting efficacy of over 80% with favourable short term safety profiles. IMT is endorsed by the National Institute for Health and Care Excellence as well as several consensus guideline publications and professional associations, such as the British Society for Gastroenterology. Beyond CDI, IMT has shown promise in a remarkable number of intestinal and extra-intestinal diseases, such as ulcerative colitis and metabolic syndrome. Perhaps unsurprisingly, academic, patient, clinical and industry interest in IMT has increased exponentially in recent years. In June 2020 there were 369 studies listed on clinical trials.gov that featured the term 'FMT' in the study title or intervention. In contrast, just 13 studies were listed on the same platform in 2013.

IMT is also, arguably, the most effective and best validated tool for understanding if specific microorganisms lead to therapeutic benefit in a particular patient population. In depth compositional and functional analysis of the donor derived ecosystems transferred through IMT coupled with in depth analysis of the recipient's microbiome allows researchers to discover individual taxa that mediate particular phenotypes and patient responses. These taxa may represent promising new therapies that could be developed as Live Biotherapeutic Products (LBPs). There is precedence for this IMT enabled patient first discovery strategy being implemented in the UK. For example, Microbiotica Limited's lead LBP asset in Ulcerative Colitis was designed based on data generated from an IMT study.

Historically, the intestinal microbiome material transferred through IMT was obtained and processed in a relatively crude manner using non-standardised processes within unlicensed facilities and governed by an unclear regulatory environment. However, in recent years multiple influential competent authorities including the Food and Drug Administration and the Medicines and Healthcare Products Regulatory Agency (MHRA) released guidelines and legislation classifying intestinal microbiome material and

minimally manipulated derivatives as medicinal products. This regulatory clarity spurred significant interest in the area from entrepreneurs, the pharmaceutical industry, investors and private and public markets, who are now developing a new generation of standardised microbial therapeutics, termed intestinal microbiome medicinal products (IMMPs) for use in microbiome restoration.

The UK is well positioned to capitalise on the substantial and growing IMT and IMMP opportunity. The country benefits from unparalleled IMT enabling infrastructure that includes several MHRA licensed Good Manufacturing Practice (GMP) compliant manufacturing facilities (e.g EnteroBiotix Limited, Guys and St Thomas' NHS Foundation Trust, University of Birmingham), a clearly defined regulatory environment, several pioneering ongoing and completed IMT studies, such as STOP-COLITIS and the PROFIT study, service providers enabling donor screening and an established industry presence in the form of EnteroBiotix Limited. The UK also benefits from globally competitive capabilities in microbiome-host analysis that enable reverse engineering of bacterial signatures associated with a phenotype of interest.

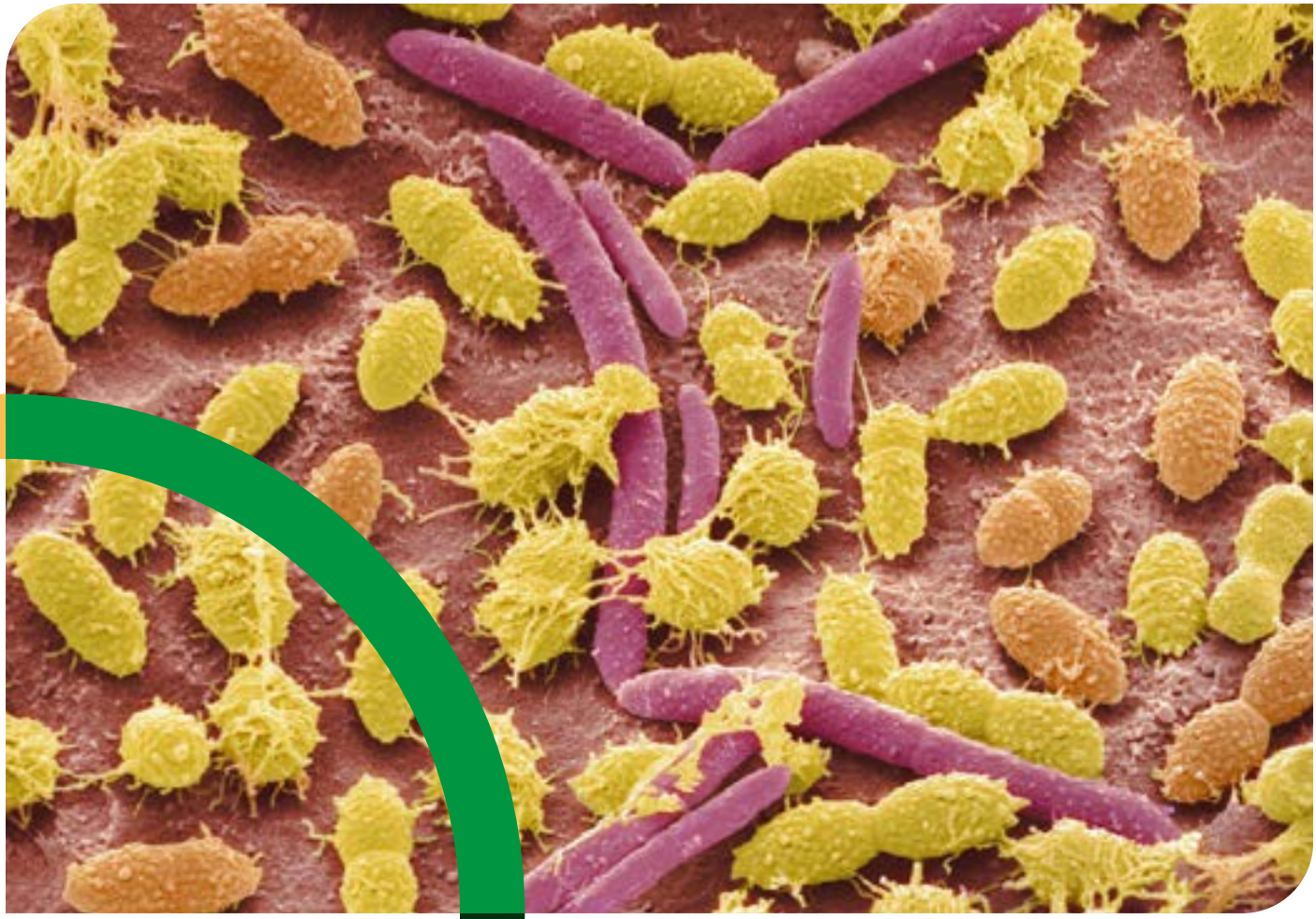
Intestinal Microbiome Medicinal Products (IMMPs)

IMMPs are standardised donor-derived microbial formulations that are manufactured using controlled starting material obtained from adequately screened donors that is processed using validated and reproducible methods in accordance with the principles of Good Manufacturing Practice (GMP) under a license from a competent authority. IMMPs can only be released for clinical use once the product is deemed to have met specific release criteria through validated analytical methods. These are key differences between an IMMP prepared using an industrial process and material prepared for contemporary intestinal microbiome transfer (IMT).

IMMPs are the most advanced class of microbiome-therapeutic. In Q2 2020, two US-based entities reported positive top-line efficacy data from late-stage clinical trials investigating IMMPs in *C. difficile* infection (CDI).

These results have validated the microbiome as a therapeutic target that can be successfully modulated through IMMPs. The results also support the notion that early, investigator sponsored IMT studies can provide useful proof of concept and pave the way for larger, industry sponsored trials of IMMPs that ultimately support marketing authorisation applications. Multiple industry sponsored studies are now underway in populations of patients that have successfully been treated through IMT.

The UK's IMT enabling infrastructure positions the country to become leaders in translational IMT research that leads to the development of IMMPs. Other assets, such as an existing industry presence (EnteroBiotix Limited), a National Health Service that has experience in supporting interventional IMMP clinical trials and well-defined IMMP regulatory framework governed by the MHRA, make the UK a highly competitive hub for IMMP drug development and ultimately, commercialisation.



Section 2.

Live Biotherapeutic Products and Other Therapeutic Modalities

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Section 2. Live Biotherapeutic Products and Other Therapeutic Modalities

Summary:

- Funding should be directed towards larger multidisciplinary programmes (integration of UK's best KOLs in Microbiome and KOLs in target disease areas).
- Programmes should have strong strategy/translational focus with knowledge of competitive landscape in target markets.
- Microbiome-focused areas of high interest Oncology, Neurobiology, Women's Health and Respiratory Diseases.
- Need to be clear on differentiation at the outset.
- Need to establish accelerator/incubator hubs (incl. advisors, investors, pharma, biotech), e.g. within the Quadram Institute.
- Ensure clarity on IP in the context of start-up creation.

Strategic Importance and Timing

In 2013 there were approximately 12 microbiome companies (Olle et al. 2013). Today there are hundreds (>300) but only a handful have incorporated in the UK.

The microbiome industry continues to grow globally, with major Pharma engagement and an estimated investment of almost $3bn. There are currently thousands of ongoing clinical trials evaluating microbiome products in infectious, inflammatory, autoimmune, neurological diseases and in cancer.

Two very recent events have succeeded in galvanizing the microbiome industry and are predicted to drive more financing and commercial activity.

1. The phase III success announced by Seres Therapeutics has triggered significant interest from all sectors, from venture investors new to the microbiome field to pharma that adopted the waiting game for the first signs of phase III clinical validation of microbiome-derived products.

2. Together with the current COVID-19 pandemic and the global race for therapeutics and vaccines, the importance of investing efforts into understanding the Microbial World We Live In has never been more obvious and essential.

Microbes impact human health – they drive disease, but equally importantly they play a role in disease management and prevention.

Scientific versus Translational Impact coming from the UK

The UK is making significant scientific impact in the microbiome field, coming in 3rd position, behind US and China in terms of publications. The top 3 UK institutions publishing microbiome related work are Imperial College London, King's College London and University of Oxford.

However, the UK is lagging behind the EU and USA in terms of translational impact, potentially missing a significant opportunity both economically and from a healthcare perspective. There is an urgent need to create an environment that leads to more translational opportunity, such as more spin-outs and start-up companies.

So how can the UK increase its commercial impact in the therapeutic microbiome space and what are the priority areas in which it can compete given the already global competitive microbiome landscape? How can the UK differentiate itself?

Moving beyond IMT/FMT/IMMP

The competitive landscape in IMT/FMT is currently dominated by companies based in Europe and the US and includes Seres Therapeutics, Finch Therapeutics, Rebiotix and Maat Pharma to name a few. As a prequel to the discussion around other therapeutic microbiome modalities, it is worth noting that while IMT/FMT and IMMPs have potential therapeutic utility and are recognised as a treatment for recurrent CDI, likely to gain market approval in 2020-21, a broad range of efficacy rates have been reported. One potential explanation for this range of efficacy is the variability in donor derived-starting material.

So, a key question is what is the long-term future of IMT/FMT-like products? Many of the established front-runner IMT/FMT companies, including Seres Therapeutics are now pursuing the development of defined microbial products (microbiome products of defined purity, identity and potency) to improve and extend the therapeutic options for treating or preventing human diseases. Whilst IMT/FMT/IMMP represents the first generation of microbiome therapeutics, providing substantial benefits to patients and paving the way for the field, in the longer-term we are likely to see the emergence of potentially superior microbiome products in the form of defined microbiome-based products.

The Future is in Live Biotherapeutic Microbiome Products and Other Modalities

Currently, the Food and Drug Administration (FDA) and the European Pharmacopeia (Ph. Eur.) recognise medicinal products containing living micro-organisms as Live Biotherapeutic Products (LBPs). LBPs are being developed either as single bacterial strains or as multi-strain consortia. This type of product is defined as 'a biological product that:

1. Contains live organisms, such as bacteria

2. Is applicable to the prevention, treatment, or cure of a disease or condition of human beings

3. Is not a vaccine and which excludes faecal microbiota transplants and gene therapy agents

These products have emerged following a number of research approaches and include:

Bottom-up systematic screening for function approaches:
For example, screening bacterial isolates either individually or as consortia for functional properties to promote SCFA production such as butyrate, to attenuate inflammatory response or to induce immune effector cells or regulatory cells, such as Tregs or CD8 T cells.

Top-down approaches:
Products have been generated from in-depth analysis of the microbiome signatures following IMT/FMT interventions which correlate with positive patient response.

Ecology Approach:
New approaches using mathematical modelling and ecosystem approaches to product design (e.g. Kevin Foster's work at the University of Oxford).

Many of the leading microbiome biotechs have developed defined proprietary LBPs, obtained validation using industry-robust preclinical mouse models of disease, for example in IBD, metabolic diseases such as T2D, in neurological diseases such as Parkinson's and in oncology and some have progressed to clinical trials. So, several questions arise:

1. Is there room for more commercial start-ups and spin-out companies focussed on LBPs? And, if so...

2. Does UK microbiome science offer an advantaged position?

Overcoming the limitations and weaknesses of microbiome data produced over the past decade – an opportunity for the UK?

For almost a decade the emphasis of microbiome research has been on low resolution taxonomic characterization of human stool microbiomes i.e.

1. Comparison of healthy versus patients or

2. Responder versus non-responder with limited investigation of function.

Furthermore, many of the studies have relied on small clinical cohorts which are not fit for purpose and are not powered to provide meaningful data.

The field is concentrated around infectious agents such as C. diff, Adherent Invasive *E.coli, K.pneumoniae* and inflammatory diseases, in particular IBD. While limited mechanistic insights do exist, too much of the current research effort is focused on SCFAs.

The field is bacteriome centric and bacterial strains or consortia are administered orally without due consideration of their niche specificity. There has been virtually no attention to the virome and mycobiome and consequently, there has been no attention to the biological and physiological importance of trans-kingdom interactions.

What can the UK do better and how can it become a major player in the microbiome field/ industry and thereby attract VC and big pharma investment?

Building on a decade of progress in the field and performing high resolution microbiome analyses at scale:

The UK is leading in microbiome sequencing and analyses. As an example, Microbiotica, a company based at the Wellcome Sanger Institute near Cambridge, built on the research and intellectual property developed by Dr Trevor Lawley, has created a microbiome platform that is unique and is only challenged by the work/platform of Eran Segal of the Weizmann Institute and Day Two. Whereas Segal has amassed microbiome metagenomic data of >30,000 individuals, Lawley has invested in culturing and sequencing the human gut microbiome (including previously uncultured bugs) and hence providing the ability to accurately map metagenomic data from the gut with unprecedented accuracy. To build on this USP, Microbiotica needed to scale their platform through access to robust clinical cohorts and through Cancer Research UK (CRUK) , are making progress in achieving this goal.

This approach can be considered as the standard required in understanding the therapeutic potential of microbiomes at other body sites such as the:

- Lung Microbiome – a major focus due to COVID-19
- Vagina/Urogenital – an emerging market opportunity with major unmet need
- Tumour-specific microbiome - cutting edge discoveries relating to efficacy of immunotherapies

Co-ordinated research, multi-centre and multidisciplinary

Multi-Omics and at scale:
Taxonomic mapping of metagenomic data to strain level resolution is important. Strain matters (e.g. C. diff both commensal and major virulent strains). This approach will yield the next generation of LBPs with superior function. However, the microbiome field is now alerted to functionality, i.e. generating insights beyond SCFA; this is already yielding new data on bile acids and novel neurotransmitters generated by gut bacteria and so much more focus is now on metabolomics such that the NIH is about to invest millions into integrating Omics.

Major workshops in the US have brought world leaders in microbiome and metabolome together in recognition of the immediate need for integration of these disciplines. The UK is extremely well-placed to capture a lead through combining its multi-omics expertise and at scale.

Time for Change – To be competitive a new funding strategy is needed

Microbiome research in the UK is mostly supported by small individual grants. This has not delivered the commercial impact seen in the US and the EU.
The template for further funding needs to be revisited.
Need for fewer but larger grant funding that enables:

- Scaled studies - access to large clinical cohorts
- Integrated omics platforms (to maintain a competitive edge internationally)
- Bioinformatics - AI-ML
- Bacteriome, Virome, Mycobiome – inter-kingdom biology
- Infrastructure – fast track discovery – moving beyond the Petri dish

A Venture Capital Perspective

It is worth highlighting that ultimately for translation of microbiome research into commercial success, the grant funding cannot only cover the early stages of research but has to also cover the more translational aspects of therapeutics development. This is especially true in the context of microbiome where a lot of VCs have undertaken early stage investments when the microbiome first became "on trend" without a deeper understanding of this space. Unfortunately, this has now resulted in higher bars to be met for VC investments into next generation companies; even though they are more sensible of course, they have a harder time securing investment. Having had their fingers burned in previous investments in these novel modalities, VCs are now looking for more de-risked approaches coming out of academia. Conversations with VCs have revealed that most of them require experimental evidence that goes far beyond proof of concept work but is more akin to pharmacokinetics and pharmacodynamics studies of drug discovery projects, they also tend to want to see more data around process development and manufacturing (a similar picture to what is currently ongoing in the cell therapy space).

Novel therapeutic targets – this is the future and route to differentiation

Current drug pipelines and market trends reveal a number of novel therapeutic target opportunities:

a. Microbiome and Oncology

The interface of microbiome and oncology could be a particularly promising space to invest in to enhance translation of early stage research into commercial products. There is a really good research base across both areas within the UK and cancer in particular is a space with a lot of translational activity driven forward by the disease charities such as CRUK.

There are two very exciting areas emerging which link the two fields:

1. The microbiome of cancer itself. Tumours create their own microenvironment with the body which has been shown to be susceptible to bacterial colonization as they thrive under hypoxic conditions. These can potentially be exploited as LBP strategies.

2. The gut microbiome has been shown to influence the efficacy of novel cancer drugs, most importantly check-point inhibitors. Understanding the microbiome composition that will ultimately lead to stronger success of checkpoint inhibitors is hugely attractive from a commercial point of view and big pharma players are expressing an interest in early stage approaches.

b. Microbiome and Neurology

The gut microbiome has been implicated in several aspects of brain function from appetite, mood, gut disorders including IBS to more severe disease conditions associated with brain function such as Parkinson's disease (PD) and Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and Multiple sclerosis (MS). Exactly how the gut microbiome impacts brain function and conversely how brain function impacts gut function is not fully understood but factors such as microbiome dysbiosis, leading to leaky gut and blood-brain barrier, in the setting of elevated inflammatory cascades and other pathological immune effector mechanisms are thought to play a key role. As with the microbiome and oncology, some of the best groups in these two broad disciplines are UK-based and multi-disciplinary engagement could provide a much more effective translationally-focused approach to start-up creation. The major drug pipeline for PD is in small molecules working through conventional PD mechanisms such as dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, catechol-o-methyltransferase (COMT) inhibitors etc. Hence new approaches should be differentiated from the existing pipeline and in many ways mechanistic insight of the microbiome should generate such outcome.

c. Microbiome and Women's Health

Focus on microbiomes other than the gut is also increasing. For example, data is emerging supporting the impact of the cancer-specific microbiomes on cancer risk and prognosis, or modulation of skin microbiomes and alleviation of acne or psoriasis and also of significant interest is the health of the urogenital tract.

Specifically, in Women's Health there is interest in addressing many of the infections that plague women for which there is a significant unmet need, and which are currently treated with countless antibiotics. Again, the UK is well-placed with significant ongoing effort to characterise these ecosystems with strain level precision and develop new approaches from phage-based therapies to LBPs in treating a variety of conditions from bacterial vaginosis to pre-term birth and infertility. Currently, the number of microbiome companies operational in this area are fewer than in gut microbiome and hence this could be considered as a priority area.

d. Microbiome and COVID-19

The current COVID-19 pandemic highlights the need to support frontier challenging scientific efforts to dissect how the microbiome (viruses, bacteria, fungi etc) impact human health. Currently, there are 37 million cases of coronavirus globally (as of Oct 2020). The virus SARS-CoV-2 triggers an extreme range of human response varying from asymptomatic carriage to severe disease, with the latter requiring hospitalization and invasive mechanical ventilation and resulting in an estimated mortality of 15%.

Factors such as genetics (e.g. ACE-2, type 1 interferon polymorphisms), age, gender, pre-existence of co-morbidities such as obesity and diabetes, and the heterogeneity in immune response to infection, all contribute to overall disease severity. In efforts to understand the variation in response and the appropriate course of immediate treatment, several high impact studies have reported that hospitalized patients display very distinct immunotypes ranging from mild to excessive immune cell activation (cytokine storm, T and B cell responses) and that both lung and gut symptoms occur. Given the demographics of high-risk patients and evidence that immune dysregulation and microbiome dysbiosis are fundamentally linked, international interest has focused on dissecting the contribution of both the lung and gut microbiomes and the importance of the lung-gut axis in dictating the immune response to COVID-19. The following research priorities are of particular importance and prominence : 1) viral infection in the context of microbiome dysbiosis 2) viral and bacterial transmission and leaky gut 3) heterogeneity of the human immune response (innate and adaptive) in context of viral/bacterial infection are areas of high research priority.

For each of the above areas, it is very important to integrate experts across disciplines e.g. microbiome scientists working with clinicians in oncology, neurology, gynaecology and respiratory viral infection.

Drugs from Bugs – New Therapeutic class of Medicines

Natural Products and Biosynthetic Gene Clusters:
Several hundred natural product drugs that are used today in patients have been sourced from complex microbiomes such as those found in soil. There is renewed interest in examining other microbiomes for novel drug discovery, in particular human microbiomes, given the coevolution and adaptation between host and microbe.

Currently in EU and the USA there are a significant number of companies actively screening microbiomes for human drug discovery including Enterome, Second Genome, Lodo Therapeutics, LifeMine Therapeutics, Deepbiome and VastBiome. Some of these companies are now in the clinic. The most recent addition, to this focused group is a Flagship Ventures company called Empress Therapeutics which is focusing on metagenomic data sets, AI/ML to turn essential microbial products into cancer and immune modulatory drugs.

Molecular mimicry:
Micro-organisms express molecules that are in many ways host mimetics and which modulate diverse host signalling pathways, from cell cycle to apoptosis, immune and inflammatory signalling. They are thought to have been acquired by microorganisms through either horizontal gene transfer from the host or through convergent evolution. There is also a class of bioactives that actually lacks sequence homology to the native host molecules but which exhibit strong structural mimicry and biological potency.

To investigate the functionality of the massive diversity of chemistry and biological molecules, it is necessary to express these drug-like entities using microbial chassis and to screen for function using a high throughput system. This approach to screen complex microbiomes has already successfully drawn in big pharma with partnerships including Genentech and Lodo Therapeutics; Enterome and Takeda.

The UK is well-placed to lead Microbial Bug to Drug discovery

With high resolution metagenomic sequencing and the ability to sequence deeper, with higher accuracy at affordable costs, analysis of the human microbiome is now pushing the frontiers and decoding the so-called "dark matter" which is the vast number of uncultured microbes for which there is no knowledge of function.

This progress and trend was featured in Nature 2020 this year as researchers forge ahead to tap into this novel microbial diversity.

Importantly, "dark matter" is not just a feature of metagenomic data, it is also a feature of metabolomics data and with the current trends in data integration this is a great opportunity for the UK.

The UK has arguably, the best sequencing facilities and metabolomics centres in the world e.g. Imperial College London.

Similarly, the growth in synthetic biology capability combined with high throughput screening capability utilizing either cell-based, membrane-based or human organoid-based can accelerate testing of large numbers of chemically-diverse and biologically-diverse compounds.

The hit to lead and lead optimization knowledge within the UK is also highly competitive and could potentially be leveraged to address this opportunity.

Hence this is an area of activity that should be prioritized in the UK and requires large funding and multidisciplinary inputs.

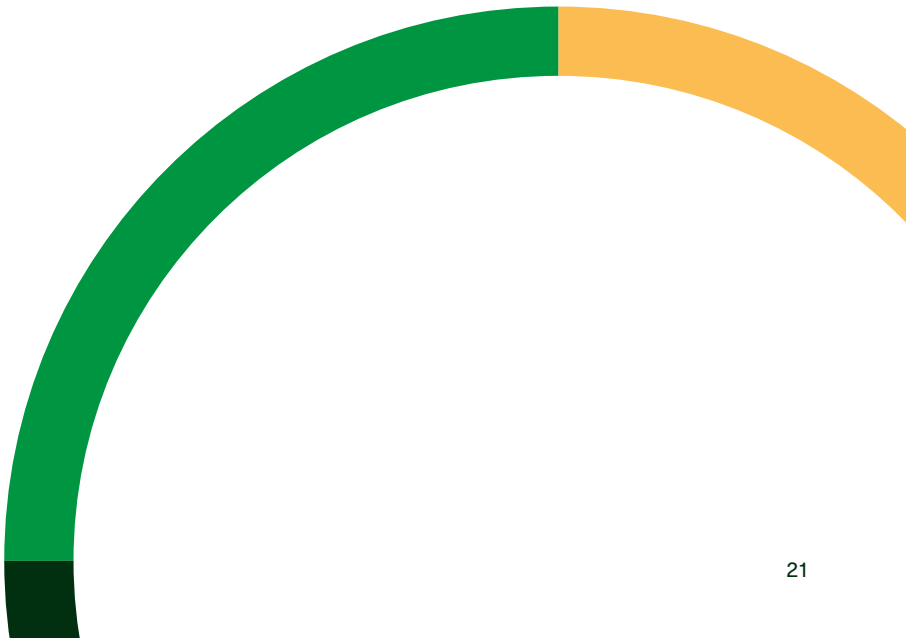
Microbial engineering delivering therapeutic cargo and development of real-time biosensors

Significant opportunity exists in engineering biology, e.g. Chain Biotech. There is also a major interest in developing microbial diagnostics for real-time monitoring gut health and potentially organ-specific health.

Microbial Ecology and co-evolutionary outcomes impacting the host– The Next Frontier

Microbiomes are highly complex and to understand the host impact it is important to consider the microbiome as an ecosystem occupying distinct body sites and ecological niches. Mathematical modelling and tools from theoretical ecology are key to understanding the health/host impacts of microbiomes. This area is considered an emergent area in microbiome science and potentially the next frontier required to fully understand and exploit the biological functions of the human microbiome. The focus here is more on the evolutionary and ecological challenges that confront the microbiota including those arising from competition with other microbes and the influences of the host, including the effects of innate and adaptive immunity (Foster et al. 2018).

The UK is well-placed to further develop and exploit this area with expertise from the University of Oxford.



Section 3.

Personal Care and Hygiene

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Section 3. Personal Care and Hygiene

The microbiome, its composition, function and modulation directs everything from underarm malodour, to dandruff, to oral health, skin condition, acne, eczema and hygiene both in terms of innate immunity and community transmission of bacterial and viral infection and within the domestic environment.

As such, microbiome science underpins a Personal Care and Hygiene sector valued at over £10Bn[1,2] in the UK and over £400Bn[3,4] in global annual sales supporting thousands of jobs across across the UK. Moreover, more than 50% of the UK population suffer from microbiome-associated skin ailments every year[5] and these represent the most frequent reason for people to consult their GP with a new problem with 24% of the population consulting a GP because of a skin complaint[6,7] placing a substantial burden on the NHS with £723m spent each year on primary care skin consultations[8] and £50m per year on childhood caries[9].

The use of consumer products makes a tangible real-world contribution to meeting these challenges for example by the use of oral hygiene products reducing the need for caries treatment by an estimated 19%[10] and enhancing the quality of life and body confidence of people with cosmetic and clinical skin conditions. Furthermore if left untreated cosmetic conditions such as gingivitis can lead to serious clinical pathologies such as periodontitis[11,12] and an increased risk of type 2 diabetes[13] thereby placing further strain on the healthcare system.

Advances in microbiome research are revolutionising the scientific, commercial and public understanding of how the microbiome contributes to wellbeing and hygiene; these advances are also opening up new opportunities for technology innovation as well as new consumer sectors such as self-care, personalisation and diagnostics.

Through a combination of its strong academic research base, role as an R&D centre for global consumer goods companies, the increasing number of UK entrepreneurial microbiome start-ups and the UK's leadership in market facing microbiome innovation[14], the UK is well placed to move into a leading position in translational microbiome research, creating market leading globally orientated export technologies.

Outside of the UK we are already seeing major public investment in Personal Care and Hygiene microbiomics, such as the state funded Asian Skin Microbiome programme in Singapore and characterisation of the skin microbiome through the US led Human Microbiome Project and National Microbiome Initiative and the EU funded Horizon 2020 initiatives and the Microbiome Support project focussed on coordinating research, policy and infrastructure to develop the microbiome economy.

The commercial opportunity of the Personal Care and Hygiene microbiome has been recognised by leading UK based and non-UK product manufacturers and suppliers.

In the UK companies such as Unilever, Reckitt-Benckiser and Croda have made significant public investments in microbiome research, whilst internationally, consumer product manufacturers including Procter & Gamble, Nestlè, L'Oreal, Johnson & Johnson and Beiersdorf and ingredient suppliers including Bayer, DSM, BASF, and Givaudan have all invested significantly in microbiome technology start-ups, academic collaborations and technology incubators in the USA, Asia and Mainland Europe.

However despite the importance of the Personal Care and Hygiene microbiome to UK export led growth, employment and the individual wellbeing of consumers, the sector has not so far been explicitly recognised in UK research strategy, science education, inward investment and small-tech sectors.

For the UK to remain competitive on the global stage and emerge as a leader in Personal Care and Hygiene microbiome research and innovation it is critical that the following areas are prioritised for the skin, oral and home microbiomes:

- **A national network of commercial and academic microbiome innovators**
  - Communication forums connecting research groups and commercial innovators.
  - Improved co-ordination between academic microbiome research and UK business innovators.
  - Collaborative problem solving aligned to commercial opportunities.

- **Stimulate the creation of centres of excellence for microbiome research and translational innovation**
  - An accelerator for translational microbiome technologies and techniques.
  - Prioritise key translational and commercial opportunities in skin, oral and domestic microbiome.
  - Training the next generation of microbiome scientists within a global priority research area.
  - Increased public education on the importance of the microbiome.

- **Strategic funding to address core underlying scientific challenges**
  - Large cohort and longitudinal epidemiological characterisation of the human microbiome.
  - Effective national biobanking of microbiome samples as a resource to stimulate innovation.
  - Integrated omics to unlock functional interactions between human wellbeing and microbiome.
  - Investment in bioinformatics, computational biology and AI to decode large scale bio-datasets.

- **Encouraging microbiome entrepreneurship**
  - Establishing business incubators to promote and nurture UK small tech microbiome companies.
  - Business and commercial training for new-tech and SME innovators.

- **Encouraging a regulatory framework that facilitates UK innovation**
  - Clarity on the UK regulatory status of consumer product microbiome innovations to unlock research and commercial investment.

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Section 4.

Nutrition and Wellbeing

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Section 4. Nutrition and Wellbeing

Microbiome modulating diets and food ingredients make major contribution to the health and wellbeing of UK consumers

The microbiome composition (of the oral and nasal cavity, the skin, the gastrointestinal and urogenital tract) and/or function have been identified as a significant variable in defining human health. Microbial dysbiosis and/or aberrant microbiota functions have also been implicated in various disease states whereas a healthy microbiome based on a high diversity of microbes has been linked to gut, immune, metabolic and cognitive health.

Furthermore, the importance of establishing a healthy infant microbiome for health status later in life has received a lot of attention and it is now understood how the seeding and development of the microbial communities in early life of humans differ among individuals based on delivery mode, gestational age and diet.

Diet is one important means of shaping a healthy microbiome and thus microbiome modulating foods and their constituents (e.g. probiotics, prebiotics and fibres) make major contributions to UK health and healthcare savings. Probiotics, for example, have been demonstrated to significantly reduce the impact of upper respiratory tract infections[1,2]. The economic benefit of probiotics in this context equated to savings of between €14.6 million (YHEC) and €37.7 million (Cochrane) in France and USD4.6 million (YHEC) and USD373 million (Cochrane) in the US [3, 4]. For the UK it is likely that the magnitude of impact would equate to between 40-80 million USD or including productivity loss USD280 million per year. Furthermore, reducing constipation by increasing dietary fibre intake is estimated to save £127 million in the UK[5].

In 2019, total sales of probiotic supplements, probiotic yoghurt and sour-milk products on the EU market were equal to USD 10,217.6 million. The EU was the top global market for probiotic yoghurt and supplement sales until 2009, but now ranks only third in sales, after China and the US[6].

The global market continues to grow (4% growth YoY on average forecast 2019-2024) but projections indicate that the probiotics market in the EU has slowed[7]. The UK together with Italy were estimated to be the two biggest probiotic yoghurt and dietary supplement markets in Europe in 2017[7]. The strengths for microbiome related consumer healthcare in the UK include numerous world-leading academic institutions actively engaged in researching microbiome-modulating ingredients combined with numerous UK manufacturers focused on marketing science backed products. Additionally, current opportunities include: government interest in microbiome science to enhance national health and wellbeing, solutions to reduce the burden on the NHS, and enhancing healthcare practitioner's (HCP) understanding of the evidence and potential of microbiome modulation.

The weaknesses in this area include: challenging regulatory restrictions, difficulty in defining a healthy microbiome uncertainty around the mechanism of action, and effect sizes that are sometimes small or supported by inconclusive evidence. Threats to advancement in this stream include competition from products that lack an evidence base and regulatory uncertainty that hampers investment in research.

The UK is in an exciting position to realise the benefits of microbiome modulation with research centres such as the Quadram Institute along with advancing understanding of personalised microbiome care and whole genome sequencing and omics technologies. The top three priorities where the UK is well positioned for success through microbiome science-based consumer health solutions include:

1. **Immunomodulation**
   - Infant immune system development (e.g. prevention of atopic conditions).
   - Infection prevention throughout the life cycle (including viral Upper Respiratory Tract Infection).

2. **Gastrointestinal health**
   - Functional constipation.
   - Irritable bowel syndrome.
   - Prevention of antibiotic side effects (e.g. Antibiotic Associated Diarrhoea).
   - Infant colic.
   - Viral gastroenteritis.
   - Lactose intolerance.
   - Non-coeliac gluten sensitivity.

3. **Emerging areas**
   - Microbiome-gut-brain axis.
   - Metabolic health.
   - Healthy ageing.
   - Women's health.
   - Gut-skin axis.

Additional research investment in microbiome science can further boost consumer health and wellbeing in highly relevant health benefit areas

A key barrier to innovation and HCP support is perceived lack of consistent efficacy data and thus government co-investment to facilitate large, robustly designed, multi-centre trials is needed. Furthermore, developing greater opportunities for collaboration between industry and academia, and enhancing educational reach to both HCPs and consumers would also be advantageous.

The current regulatory landscape for microbiome modulating ingredients in the UK/EU limits the communication of published research findings to consumers. This situation discourages many companies from making more substantial investments required to advance research and development in the field. Refining the process/mechanism for the evaluation of scientific research in order to facilitate and validate product claims based on such research would be welcome.

Ensuring the UK is an attractive place to carry out microbiome research is also essential. To achieve this aim, provision of readily accessible funding/incentives for UK-based research and the creation of a central register of UK universities interested in microbiome research and their specific interests is needed.

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The Human Microbiome

A New Frontier in Medicine, Consumer Health & Nutrition, Personal Care & Hygiene

HUMAN MICROBIOME:

- Trillions of microbial cells
- Millions of microbial genes
- Tens(+) of thousands of metabolites
- Tens of thousands of microbial strains
- Thousand(s) of microbial species

Other Important Microbiomes:
Oral, Skin, Vaginal

Preclinical & Emerging Clinical Evidence Points to Utilities to Treat or Prevent:

- Infectious Diseases, e.g. rC. difficile
- Inflammatory diseases, e.g. Crohn's, UC
- Metabolic disease, e.g. Obesity, Type 2 Diabetes
- Cancer, e.g. ICI enhancement
- Autoimmune diseases, e.g. T1D, Multiple Sclerosis
- Neurological diseases incl. Depression, Parkinson's
- Skin and dermatological conditions
- Vaginal infections

Potential Microbiome Products:

- Intestinal microbiome medicinal products – IMMPs
- Live biotherapeutic products – LBPs
- Ant/agonists of microbiota drug metabolism
- Microbiota-derived drugs incl. small molecules
- Targeted antimicrobials, e,g, phage and peptides
- Probiotics, Prebiotics. Postbiotics, Parabiotics
- New biomarkers for discovery and diagnostics

Section 5.

Animal Health and Nutrition

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Section 5. Animal Health and Nutrition

The farmed, equine, companion/working animal, and aquaculture sectors add significant value to the UK economy as well as contributing to human health, fitness, and wellbeing.

Our farmed animal sector, worth £14bn annually[1], faces mounting pressure to feed a growing population, compounded by increased pressure on producers for more sustainable approaches with a focus on protecting animal health and welfare, as well as human health and the environment.

Ruminants, when used to transform fibrous feedstuffs produced on land that is unsuitable for primary cropping, can be net contributors to the supply of human-edible food. However, whilst ruminal fermentation is critical to make use of fibrous substrates, it also has deleterious environmental consequences because of greenhouse gas emissions. For the ruminant livestock sector to grow, new technologies must be developed which simultaneously decrease the environmental footprint and boost productivity. Recent studies suggest that rumen microbiome variation can explain ~60% of the variation in cattle productivity demonstrating direct linkage with productivity and profitability.

The monogastric farming sector has focused on improving feed efficiency and reducing production days. Research has highlighted the importance of the microbiome in meeting performance objectives and reducing susceptibility to disease, particularly in systems utilising fewer antibiotics/antimicrobials. The UK was an early adopter of restricted antibiotic use (UK 2019 One Health report highlighted a 35% reduction in animal antibiotic consumption between 2013 and 2017), but, with increased growth rates and pressure on the digestive physiology, intestinal health issues and zoonotic infections threaten industry performance. The farming sector must remain competitive in a global market as the UK strives to establish itself as an independent player post Brexit. Innovation is essential to maintain UK internal and export market shares and to maintain UK competitiveness and sustainable high welfare system standards.

There are an estimated one million horses in the UK, in a sector that contributes over £8bn annually to the UK economy and is a major employer. Whilst a few are used for draught power and there is a vibrant breeding and horse racing industry, the majority are used for leisure. Changes to the equine gut microbiome due to diet, drugs, stress, and various management practices are linked to many important conditions in horses (e.g. obesity, laminitis, colic). Colic has been estimated to occur in between 4 and 10% of the equine population and the cost of surgical treatment varies from £3,000 to £9,000 per animal. With a greater knowledge of the microbiome a more proactive approach to gut health could improve welfare and enable the UK to be a world-leader in the production of novel dietary health interventions to support equine health and performance.

Pets represent an important part of the community with household spending on veterinary and pet services totalling over £5bn annually[2]. Pets and companion animals including equine provide a wealth of social benefits and enrichment to the UK economy and society. Behavioural habits involved in caring for pets serve to engage owners in social activities, and in physical exercise as well as reducing loneliness and creating connection between owners. Direct economic impact arises through feed and welfare and equipment purchase and the enhancement of health in both the pet and pet owner (£2.5bn annually is spent on pet food and £2.1bn annually on veterinary or associated pet services)[2]. Pet, and companion including equine, ownership has also been linked directly to positive human outcomes[2], including greater microbiome diversity, increased fitness, improved mental well-being and enhanced learning. As with other animals, the microbiome within the gut and other body surfaces plays a major role in the health and welfare of our pets and by extension their owners.

UK aquaculture has not expanded at the same rate as the global sector despite evidence that aquaculture makes a significant contribution to the UK economy and food security. The estimated gross added value (GVA) of aquaculture enterprises in the UK is £375m[3]. Numerous reasons exist for the reduced competitive performance of UK aquaculture, but key issues include parasite and microbial infection within farmed stock which require a holistic approach to the multiple microbiomes associated with the environment and internal plus external surfaces of the fish. Effective management of these challenges requires understanding of the factors that control these linked and interacting microbiomes; how they affect fish health and how they can be manipulated in environmentally acceptable ways.

There is a clear opportunity for the UK to show leadership in developing a holistic approach that allows the companion, working, sport, leisure and production animal sectors to generate a proactive approach to enriched husbandry rather than reacting to global agricultural and socio-economic pressures.

Through a better understanding of microbiomes, their function, and consequences we will be able to improve nutrition, environmental management and enrichment as well as develop alternatives to antibiotics and other drugs. This would allow the UK to produce economically valuable new products and other innovations whilst also improving the health, welfare, and performance of our animals. The UK has significant strengths in both the commercial and academic sector which should be called upon to identify beneficial components of microbiomes to support:

Welfare: The UK benefits from some of the highest global animal welfare standards and is regarded as a world leader. Microbiomes within the animal and in the environment play a clear role in both health and disease. Through welfare friendly modulation of the microbiomes in animals and their environments the UK can improve animal health and develop new national and international brands for products and services.

Performance: With a clear focus on outcomes, a framework can be built that considers the role and manipulation of microbiomes in terms of productivity coupled with product quality in farmed animals together with quality of life and owner experience in companion animals.

Environment: The impact of both production and companion animals on the environment at a local and global scale is becoming increasingly important. Holistic studies considering animal associated microbiomes in the wider environment including both direct emissions, zoonoses and gene transfer provide an opportunity for the UK to provide global leadership in this area. A microbiome-based proactive health approach will facilitate a unique opportunity for the UK to develop outcome-based products and services. Furthermore, the UK can lead an evidence-based approaches to the development of a dietary, husbandry and genetic approach to the control of animal microbiomes enabling significantly decreased livestock greenhouse gas emissions.

Despite the impressive expertise within the UK, the microbiome research/business industry remains relatively small and significantly fragmented with limited linkages between academia and industry. Market led microbiome-innovations for enhancement of the UK economy would best be served through forming pre-competitive collaborative networks with established academic and clinical researchers. Ultimately, creating a collaborative network of UK innovators generating outcome focused research with specified deliverables and measurable economic outcomes across the companion and production animal sectors. We envisage that developing evidence-based knowledge of the microbiome linked with a thorough understanding of underpinning mechanisms of action will drive IP and innovation enabling valuable new products and services to be produced that can manipulate animal microbiomes thereby also benefiting from the enhanced productivity that such products will drive. Our workstream suggests the following areas of focus for funding bodies and innovation business leads.

Community: Develop coordinated UK based resources and training resources with a focus on:

- Working across the sectors to ensure the generation of universal truths plus animal species-specific solutions that facilitate flexible, productive answers and relevant IP and impact in a timely manner.
- Providing UK based biobanks and databases.
- Developing white papers to allow techniques and approaches to be shared.
- Promoting and permitting access to shared facilities and expertise.
- Promoting a multi-omic approach that focusses on function rather than simply taxonomy.

Culture: Develop a culture (and funding regimen) that promotes collaboration at a precompetitive level:

- Encourage UK multi-actor approaches to establish UK networks that link academia and industry post-Brexit working together with shared objectives.
- Virtual hubs that generate cross animal species consortia
- Cross and inter sector (animal species) funding that requires collaboration across centres.
- Funding that encourages, promotes, and requires samples to be bio-banked and data to be intelligently stored and facilitates in-depth innovative analysis.

Recognition: Enhance the scope of the animal microbiome for UK centric benefits:

- Building a talent pipeline that maintains and grows the UK skills base and provides resources for upskilling
- Advocate the recognition that microbiomes are unique across animals and environments but that all environments are ultimately linked
- Recognise that health, clinical and economic outcomes are ultimately linked and should be considered in a proactive one health strategy.
- Enable regular opportunities to promote knowledge sharing and build collaborations across animal species.

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The Animal Microbiome

A New Frontier in Farmed Animal Agriculture and Companion Animal Care

Animal Microbiomes:

- Monogastric microbiomes (e.g. chicken, pig, dog, cat, horse)
- Ruminant microbiomes (e.g. cow, sheep)

Harbouring a Diverse Microbial Community:

- Bacteria, archaea, protozoa, fungi and viruses
- With the bacterial phyla, - Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria - highly represented

Potential Benefits of Microbiome Science:

For Farmed Animals:
- Improved health, welfare, performance and quality
- Reduced antibiotic use and AMR
- Lower environmental impact

For Companion Animals:
- Improved health and quality of life
- Enhanced owner experience and companionship

Microbiome Product Innovation Potential:

- Live Veterinary Medicines, e.g. consortia or single strains
- Nutritional interventions including Probiotics, Prebiotics, Postbiotics, Parabiotics
- Ant/agonists of gut microbiota function, e.g. reduced methane emissions in ruminants
- Breeding for microbiome composition and function for performance, environmental, other benefits
- Microbiome-based diagnostics

Section 6.

AgriFood & Nutrition – Crop & Soil Health

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Section 6. AgriFood & Nutrition – Crop & Soil Health

A new (microbiome) frontier: strategy to maximise the impacts of plant and rhizophere research in the UK.

Understanding and manipulating the plant/rhizosphere microbiome is of strategic importance to the UK economy.
Microbiome research has signaled a paradigm shift from traditional microbiology towards genomics-based systems approaches. The driver for this initially came from the human healthcare domain and we are now seeing this translating to the Agrifood domain. The potential is enormous, but the UK needs to be able to take advantage of these opportunities in order to remain globally competitive.

Key areas of research and translation include impacts on the sustainable production of food, improvement and sustainability of the environment and the UK's market share in agritechnological products. Enhancing our understanding of the soil microbiome and its functions while eliminating detrimental practices can contribute to healthier, more resilient soils which is critical for achieving better nutritional quality food from less land with fewer inputs and interventions. It will also result in enhanced carbon capture, flood mitigation and natural attenuation of pollutants in soils.

Soil microbes drive most soil functions, but this fundamental and essential contribution is often overlooked. More broadly, the soil microbiome is also a valuable source of novel chemical and biological solutions to societal challenges which may include new antibiotics to tackle resistant pathogens and microbes and microbial products that are active against crop diseases and pests and is intrinsically linked to the One Health concept.

Competitiveness and the global bioeconomy: Environmental, economic and ecosystem impacts from understanding the plant and rhizosphere microbiome.
There are a series of drivers that support an increased focus on the plant/rhizosphere microbiome, and for which a joined-up strategy between academia and industry is essential for the impacts to be realised. With increased phasing out of industrial pesticides and herbicides and the need to develop sustainable biological solutions there is likely to be an increased focus on developing chemical free, zero carbon sustainable agriculture.

There is also an opportunity to drive support for much needed improvements in consumer habits, including both provision of safe and healthy food for plant protein production, novel crops and improved nutritional content of existing crops. Economic drivers in this area are huge, with the market for agricultural biologicals including new natural products, biofertilizers, biostimulants and biopesticides projected to reach USD 10.05 Billion by 2020, growing at a cumulative annual growth rate of 14.5% from 2015 to 2020[1].

The microbiome is crucial to support UK self-sufficiency as we leave the EU, as well as global food security and quality. Other countries are leading in the way in the field and we must catch up. Taking a larger share of the agritech economy will increase earnings from innovative naturally derived pharmaceuticals and plant protection products, and also increase employment in agriculture and supporting industries. At the ecosystem level, better understanding of the plant/rhizosphere microbiome will help to protect natural biodiversity and public goods, reduce soil loss and thus enhance potential for future farming. It will help to generate new sustainable crop germplasm and drive opportunities for better targeted and safer chemical and biological solutions to plant and human pests and diseases.

The missing links: academia-industry connections and co-ordination of our infrastructure

There are clear opportunities for our microbiome community to enable the UK to develop as a world leader in this sector (above and examples in Table 1). The UK has numerous strengths including an excellent research ecosystem of world-class scientists and labs, good access to funding as well as strategic Agritech resources at our research institutes and universities, and knowledge-based resources. Promising signs in this direction include investment in collections and infrastructure.

Top 3 priorities where the UK can succeed	Examples of new innovations characterising the UK's potential
Novel biocontrol/growth stimulation microbial products avoiding the need for chemical intervention and driving towards sustainable agriculture.	Investment in National Agri-Tech Centres including the Phenotyping and Soil Heath Facility and Controlled Environment Agriculture capabilities. These will support the emerging agritech-microbiomes sector and identify innovative and disruptive sector opportunities.
Natural product discovery and exploitation (for healthcare, better nutrition and agrichemical replacement).	New UKRI funding initiatives including the UK-Crop Cryobank, a world-first, and the UK Plant Microbiome initiative. These will establish key collections and enable their use in discovery science and applied work.
New germplasm for soil sustainability and better advice to farmers.	Natural product discovery pipelines that involve colleagues from both Universities, Companies and Research Institutes. These will enable delivery of research discoveries to industry.

However, over-regulation, lack of research and infrastructure investment, a focus on human healthcare, which often takes precedence over Agritech, and challenges from Nagoya Protocol are **threats** to our ability to take these opportunities. We must also be mindful that our talent pool of new researchers is under threat since the teaching of microbiology is only a small and somewhat forgotten component of most biological degree courses. Our **weaknesses** include a relative lack of critical research density in the UK and disconnect between applied and fundamental research communities. Funding streams are often fragmented, with restrictive short-term conditions that hinder take-up and efficiency. Routes to start-up and marketisation for fundamental science are poorly supported in much of the university sector and the cost and technology readiness of applied aspects of microbiome analysis for diagnostics limits translation.

Delivering on the microbiome for the UK: a Knowledge Transfer Network (KTN) microbiome workstream-led action plan

We therefore recommend activities in four key areas to enable maximum progress to be made:

a. Fostering closer relationships between industry and academia:

There is a critical need to strengthen the relationship with business and make it easier for business to collaborate with UKRI, other funding bodies, government, academic and other institutions in order to deliver the priorities for Agrifood and nutrition to society. This should be facilitated through greater levels of pre-commercialisation engagement between all parties to improve the alignment of research with need. Actions are to:

- Simplify and standardise agreements and administration.
- Establish a networking forum in association with Agri-Tech Centres, KTN, learned societies, initiatives, universities and research institutions to enable relationships to be enhanced, made simpler and build trust.
- Enhance the role of the Agri-Tech Centres as nexus between industry, academia and government.
- Promote short-term secondments to co-understand priorities and timelines.
- Increase visibility for linking people in each organisation, including commercial arms in research institutions and research themes in universities.

b. Increase funding access and opportunities:

Earlier and better engagement with industry to identify pre-competitive priorities will in turn enable more rapid take-up of funding opportunities. KTPs, Innovate-UK, Industrial Biotechnology Innovation Centre (IbioIC), Scottish Enterprise and others provide a good example of transferring academic knowledge to the industry sector, but need to be open to work without immediately obvious outputs, encouraging both translation and blue-skies work. Actions are to:

- Enable rapid-release pump-priming to kick-start industry-academia interactions.
- Recommend microbiome-focused calls and strategic grant funding.
- Support and nurture identification and development of pre-competitive ideas to ensure better translation from the underpinning R&D base to meet industry needs (role for Universities, Research Institutes, Agri-Tech Centres and others).
- Pilot an online newsfeed to get opportunities communicated rapidly.

c. Working together to form effective infrastructure:
Research infrastructure in the UK is good but not focused on the microbiome. Our excellent collections are not advertised and are not always available or easily shared. Barriers need to be overcome and assistance provided with respect to the Nagoya Protocol and intellectual property. Data management is incredibly important and often industry and researchers are unaware of what the data can do for them, thus we need to ensure better access to resources and expertise. Genomics and bioinformatics is very important for the Agrifood and nutrition area and the European Bioinformatics Institute (EBI) 'MGNify' is evolving to include data from plant and crop systems, but effort is still mostly focused on human healthcare. Actions are to:

- Ensure visibility and open access to data and resources via development of a UK Microbiome Portal for Agri food and Nutrition.
- Promote UK International competitiveness by gaining a seat at the interactional table, e.g. The International Phytobiome Alliance, EU MicrobiomeSupport, International Bioeconomic Forum.
- Engage with relevant stakeholders to ensure that microbiome research is underpinned with appropriate national infrastructure capabilities, such as CHAP.

d. Interoperability: developing standards and legislation:
There are no international standards specifically for microbiome research, which can reduce the confidence in data and impact on its downstream use. This is particularly important for meeting environmental and legislative standards required for due diligence declarations, the use of MTAs and the terms therein and for environmental regulation. Actions are to:

- Support a collective effort across KTN workstream to devise common standards, and linking different communities (computational scientists, lawyers, researchers etc.).
- Engage in international groups in the US and EU looking at this issue e.g. Phytobiomes Alliance, EUMicrobiome support etc.

Microbiome for the future in the UK

The KTN MIN supports development of an AgFood event for all stakeholders showcasing UK facilities, infrastructure and research, and enabling rapid progress in all four focus areas to be made. Pursuing and coordinating the recommended areas of activity will be beneficial for academia, the Agritech/private sector and for UK competitiveness.

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The Plant Microbiome

A New Frontier in Crop Agriculture

Plant Microbiomes:

- Rhizosphere (10^9 microbes per gram)
- Phyllosphere
- Endosphere

Harbouring a Diverse Microbial Community:

- Actinobacteria, Bacteroidetes
- Firmicutes, Proteobacteria
- Fungi & other eukaryotes

Microbiomes Science Targeting:

- Soil improvement
- Quality
- Enhanced nutrient availability
- Nitrogen fixation
- Pathogens and Pests
- Abiotic stress tolerance

Potential Sustainable Microbial Biofertiliser and Bioprotectant Solutions:

- Synthetic microbial communities or consortia or individual strains.
- Crop varieties bred to support beneficial microbes
- Efficient delivery systems including seed treatment and soil, root or foliar application

Section 7.

Regulatory

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Section 7. Regulatory

Advancing Microbiome Assets

'Chance favours only the prepared mind' Pasteur, 1854

Introduction

The UK is well placed to spearhead discoveries in the microbiome and translate these to marketable assets. The strength of the UK in this respect is its international reputation, world leading institutions, and research organisations, particularly in the "omics", design, informatics, and technology. These together with established manufacturing capabilities, scientific and technical networks, a steady flow of world-class graduates, and a robust start-up ecosystem are enablers of innovation. In addition, a well-established legal system and regulatory frameworks and practices exist, the quality of which have been given the highest overall country score by the Organisation for Economic Co-operation and Development (OECD)[1]. These are all vital for enabling the life sciences to derive maximum knowledge and understanding from biological, medical and environmental microbiome-related big data and to develop successful commercial assets.

Regulations are an important tool for advancing public protection and confidence when based on the principles of good regulation: proportionality, accountability, consistency, transparency and targeting[2]. Good regulation reduces business burdens, provides certainty, increases the transparency of regulatory regimes and thus supports entrepreneurship, market entry, and economic growth that, in turn, should produce high-quality employment and commercial assets.

Innovators' Hurdles

While regulatory frameworks have specific objectives to safeguard health, safety and the environment, and influence certain company strategies and activities, they can also be key factors influencing the promotion of innovation activities of companies, industries and whole economies[3,4]. Yet, there are many hurdles to ensuring fit for purpose regulations in innovative emerging science areas, such as the microbiome field. The gap between the rate of scientific advancements and the procedures intended to regulate them, often called the "**pacing problem**", is steadily growing. There is evidence that the fast pace of microbiome developments clearly challenges existing frameworks as illustrated by issues around faecal microbiota transplantation (FMT) policy and regulation[5].

The approach employed to modify or measure the microbiome is critically important as, together with intended use and claims, it is a decisive factor in how a product is regulated. However, regulations are not always easy to understand and navigate. When dealing with innovative solutions, determination of the appropriate regulatory classification, regulatory requirements and pathways are often difficult even for those with considerable regulatory experience. This is further complicated by the fact that assets from successful microbiome research can span multiple regulatory frameworks and be developed to target many different markets, for example, therapeutic, medical device, personal care, biocidal, food, feed, agriculture, animal welfare, aquaculture etc. In certain cases, the development of microbiome solutions may be novel or produced by an entirely novel approach and may not even fit easily into existing well-established regulatory routes. Understanding the right questions to ask, the scope of those questions and the information that must be provided at each critical stage to ensure appropriate advice is obtained, while developing and executing pre-clinical, clinical and chemical manufacturing control plans to support regulatory submissions and product claims, is challenging.

In some sectors, lack of standards and regulatory definitions are considered to hamper developments and lead to uncertainty. For example a regulatory definition of 'probiotic' bacteria, 'prebiotic' and 'postbiotic' is currently lacking in the food and cosmetic space. This leads to confusion. Yet, it is worth noting that use of the term 'probiotic' in association with food is generally considered a health claim in the EU which requires authorisation. It has also been suggested that the classification and regulatory requirements for agricultural and environmental microbial inoculants and bio-stimulants lack clarity[6].

Another aspect that is often called out in relation to microbiome solution development is the lack of specific regulatory guidance to aid developers interpret and apply existing regulations to their particular microbiome-related case[7,8]. The lack of a comprehensive framework within which to direct existing technology makes it very difficult to set precedents and to thereby appropriately place new and emerging technology. Concerns have also been expressed about the complexity of rules and diverse requirements that impact biobanking and research, such as the Nagoya protocol and General Data Protection Regulation, which can create uncertainty and inhibit developments. In addition, too few opportunities to engage experts, regulators and other stakeholders in open, pre-competitive discussions can hamper information exchange and slow development progress.

Future Perfect

As emerging technologies lead to new business and service models, as well as enforcing regulations, governments **must rapidly evolve** and modify regulations. This needs to be done while both benefitting and protecting citizens, ensuring fair markets and letting innovation and businesses flourish. Microbiome research is rapidly moving and boundary-challenging with immense potential to elucidate new disease mechanisms and provide new research tools, foods, feeds, diagnostics, biomarkers, targets, and therapies[8]. It is acknowledged that these advances will likely **disrupt traditional assumptions** about definitions of health and disease. Developing a regulatory environment that is well-suited to emerging microbiome developments would pay dividends by reducing time and cost to launch innovative products. It would also ensure access to innovative and efficacious products and services, such as is evident in the case of recent development of licensed FMT services ensuring availability and access to FMT medicinal products in the UK[9,10] However, as new innovations may also lead to unintended **consequences**, it is imperative that regulations evolve to ensure consumers and patients are safeguarded and protected while confidence in scientific innovation is fostered. The current UK Government is fostering agile approaches that transform the regulatory system to support innovation while protecting citizens and the environment[11].

Regulations are complex and advances in the microbiome space often challenge existing regulations and create new regulatory needs as well as opportunities. Several types of **innovation friendly approaches** to regulation could support microbiome advances. Single points of access for early and close dialogue between developers and regulators, exemplified in the therapeutic area by the MHRA Innovation office, would ensure that pitfalls are avoided[12]. Providing easy access to regulatory advice would help innovators navigate the regulatory system and understand the requirements.

While scientific guidance is being developed by interested stakeholders, further development and elaboration of **standards** and **regulatory guidances** that outline and clarify specific requirements would also greatly aid navigation of the regulatory frameworks for developers[7,13,14]. Anticipation and development of the **controls and standards** to facilitate successful product development from the initiation of idea generation to subsequent launch are urgently required and would advance the microbiome field. For example, many if not most microbiome diagnostics will be based on next generation sequencing (NGS) – targeted or agnostic – to determine the presence, absence, and/or relative abundance of tens if not hundreds of microbial taxa and/or microbial functions (e.g. genes or pathways). However, NGS as a diagnostic tool has only recently been accepted by the NHS, and currently no regulatory guidance exists for studies to establish the laboratory and clinical performance characteristics of NGS-based microbiome in vitro diagnostic (IVD) devices. Recommendations from regulatory organisations (MHRA, Notified Bodies) and healthcare stakeholders (e.g. NICE) are needed to cover the entire process from sample collection to report generation, including validation of laboratory protocols, availability of regulatory-grade databases, and how to treat superfluous sequencing information. Moreover, clarity on appropriate metrics required for laboratory and clinical performance evaluation and also associated with the marketed product is required. Hence, it is critically important to align with the above regulatory and healthcare stakeholders early in the device development on what those quality control (QC) metrics are and how they will be measured. Appropriate QC also requires alignment on and availability of regulatory-grade microbial standard reference materials. Furthermore, NGS-based microbiome IVD devices are likely to incorporate artificial intelligence (AI)-based algorithms. While NHSX has recently published policies to ensure utilisation of AI in Healthcare is done in a safe, effective and ethically acceptable manner, regulatory guidance is needed during device development and beyond on how to implement the Governance Framework. Similarly, assistance in interpreting the diverse rules and requirements relating to biobanking, which supports discovery, and conduct of microbiome and other research, would also be welcome.

Innovation systems, which drive **interaction and information** exchange between the actors in the system, are known to drive the innovative performance of industry [6,15]. Active and frequent engagement of stakeholders involved in microbiome innovation from broad and diverse backgrounds would also stimulate knowledge and insight sharing and aid future rule making development. In addition, these interactions can help innovators understand some of the pertinent regulatory issues, examples of such interactions include the EMA hosted workshop on therapeutic applications of bacteriophage and the OECD microbiome workshop[8,16]. Such approaches, which drive interaction and information exchange between the actors in the system, are known to drive the innovative performance of industry and innovation is critical for maintaining competitive advantage[15]. New Innovation Expert Groups, as outlined recently by the Government, that would support research and innovators from initiation to product development are most welcome in the microbiome space.

With global launches of assets of importance, new or adaptations to existing regulations should take account of other jurisdictions existing or proposed regulations. International collaboration on regulatory **harmonisation** would help promote regulatory convergence, maximise consumer protection, reduce barriers and burdens to trade, and ensure that products could reach several markets. Such collaboration also helps firms understand the basis for regulatory divergence and share learnings. Notwithstanding regulatory changes, increased **trust, transparency and openness** of microbiome innovations and technologies can also be fostered by Government and private institutions alike by promoting microbiome-related awareness campaigns and initiatives, such as, Quadram Institute's 'Guardians of the Gut Campaign' and Citizen Science Project 'British Gut'[17,18].

Anticipatory regulatory approaches to disruptive emerging microbiome technologies and other innovations will ensure innovations that will enhance consumers' and patients' lives while ensuring innovation flourishes. The UK is well placed to lead in the conduct of novel trials particularly related to microbiome therapeutics and diagnostics due to the strengths in emerging technologies, such as, genomic medicine and cell-based therapies, as well as the increasing use of digital systems within the NHS. Microbiome innovation and technologies can be fostered and incentivised by Government and regulators to help secure the economic and societal benefits of world-class microbiome research across the UK. Ensuring regulations, rules and good regulatory practices encourage advances that target unmet needs, mitigate any unintended consequences of the developments and are based on good regulatory principles is paramount to help secure the economic and societal benefits of world-class microbiome research across the UK. Microbiome-based technologies and their regulation across multiple areas and sectors may provide useful learnings and, indeed, a template for the development of a swift, efficient and safe regulatory framework in a number of emerging areas[19].

The opinions expressed herein, and the conclusions of this chapter are those of the authors alone and do not necessarily represent the views of their organisations.

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Section 8.

Manufacturing

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Section 8. Manufacturing

Due to the current worldwide focus on high value manufacturing for cell and gene therapies, there is a massive shortage in global capacity available for fermentation and finished dose manufacturing with the flexibility and expertise to fully exploit the potential benefits of microbial based therapeutics.

This is seriously holding back innovative healthcare companies, pioneering small biotechs and academics who are seeking to take their new products through clinical development and having a clear route through to commercialisation. Despite having pioneered the access to clinical trials for these products nearly a decade ago, and having the first MHRA/FDA inspected facility for finished dose manufacture, the UK has fallen behind the rest of Europe, US and Australia in advancement of investment into the unique manufacturing requirements needed for this fast growing therapeutic sector. This is leading to many companies seeking funding and larger scale manufacturing expertise outside of the UK.

Microbial therapeutics consist of live biotherapeutic products (LBPs) that can include bacteria (fastidious anaerobes, spore formers and multi-species consortia), viral (virus and phage) and microbially derived drug products such as peptides and spores. The diversity of LBPs requires a broad range of expertise, analytical techniques, operational flexibility and handling requirements to ensure safe and efficacious manufacture.

The needs of LBPs fall in a grey area between traditional new chemical entities and biologicals and as the regulatory pathway for manufacturing hasn't been clear it has put many contract service providers off preferring to establish capacity in areas where guidance and immediate need is more obvious, e.g. viral vector, cell and gene therapies manufacturing. Most biologics manufacturers offer only sterile fill/finish capability, which isn't suitable for these therapeutics. This translates into a need for manufacturers to be able to cross between the GMP boundaries of biologics and small molecules to come up with a hybrid solution that isn't cost prohibitive and supports the delivery of a new frontier of medical treatments.

For the UK to be able to force a paradigm shift in the approach to LBP manufacturing needs for this exciting new sector it needs to consider the following:

- Pharmaceutical development capabilities conversant in both biological and small molecule manufacture to develop bespoke approaches whilst providing low cost manufacturing capability.
- Enhanced analytical techniques and investigational tools to ensure safety, efficacy and expert understanding of critical parameters that affect therapy performance.
- Process development, scale up and small batch manufacture (fermentation and finished dose) to provide academics and start-ups with material for pre-clinical and clinical development, coupled with commercial manufacture capability to support the pipeline of products entering later stage clinical trials. Ideally, this needs to include flexible facilities capable of handling a diverse range of LBP microorganisms or microorganism derived therapeutics.
- Specific facilities for developing and optimising the formulation and lyophilisation conditions for LBPs to enhance stabilisation for further processing and strengthening supply chain handling.
- Building/further funding for dosage capabilities already in the LBP space and work already funded in proof of concept spore manufacture.

Section 9.

Biobanking

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Section 9. Biobanking

Biobanks and culture collections are integral to research and medicine, storing and distributing biological materials for research, medical and industrial applications. They are repositories of archival tissue, preservers of genetic diversity, providers of microbes for biomanufacturing and probiotics, and sources of life-saving therapeutics.

The storage and distribution of microbiome samples presents new challenges. Biobanks store a temporal snapshot of samples. Culture collections propagate and store isolated organisms. Expertise in both is highly specialised around their biological holdings, but the microbiome is a complex community of bacteria, fungi, viruses and protists. Current isolation and culture methods cannot reduce these systems to all their constituent components, but cryopreservation technology is being developed to preserve the functional potential of microbiome samples.

Microbiome data must be maximised

Microbiome research requires that samples are processed through to multiple analytical endpoints, including deep genomic, transcriptomic and metabolomic characterisation to determine who is there and how they function. Samples and derived products must be appropriately prepared and stored so they can be assayed for functional potential. Biobanks need to adapt to multi-omic profiling, capturing large amounts of data and disseminating detailed and accurate metadata. Biobanks must work closely with standards organisations, and each other, to develop agreed standards for extraction, characterisation, description and storage of microbiomes and their associated data.

UK biobanks need to share expertise

Established UK culture collections are represented by the UK Biological Resources Centre Network (UKBRCN) but microbiome biobanks and academic and privately held collections are not represented. Integrating and sharing expertise across taxonomic silos in the UK community is critical to preserving, distributing and understanding microbiome samples. In the Agrifood domain, a UK Microbiome Cryobank microbiome project has been established, a collaboration between 5 UK research institutes. Extending links to between biobanks will be essential to create a UK 'network of excellence' for addressing the challenges of microbiome storage.

Develop "next-generation" biobanks

Recent advancements in high-throughput sequencing, automated liquid handling, machine learning, single-cell analysis and microfluidics provide "research at scale". The search for microbiome-derived, functional strains to deliver targeted effects requires the ability to culture them at industrial scale and provides benefits to multiple industry sectors including medical research, agriculture and the green economy. Many organisms cannot be cultured in isolation because of some dependency on another organism, metabolite or culture condition. Using high-throughput research infrastructure to dramatically increase the number of strains that can be isolated and grown is essential. Leveraging existing investment in UK high-throughput infrastructure, and understanding the requirements of the microbiome community to advance biobanking technology will offer significant return to the UK bioeconomy through the isolation and characterisation of biotherapeutic, agricultural and soil health and food industry products.

Recommendations:

- Biobanks should rapidly engage with stakeholders across the microbiome community to understand their requirements
- Biobanks must provide integrated, cross-disciplinary, expertise to meet the needs of the UK microbiome community in order to:
  - Facilitate UK industry in developing microbiome derived products.
  - Underpin UK research activity into microbiomes.
  - Support industry in complying with regulatory processes, and support intellectual property protection.
- There must be investment to bridge existing scientific infrastructure with the biobanking community to grow expertise and develop next-generation biobanking capabilities.

Section 10.

Enabling Technologies

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Section 10. Enabling Technologies

Introduction

The field of microbiome research is highly diverse and dynamic, and involves a number of different technological areas (see schematic). These include: i: sampling technologies, such as high-throughput culturing approaches to derive extensive microbial culture collections, and model systems for microbial discovery and experimental validation; ii: measurement technologies to rapidly and accurately produce microbial DNA measurements and associated data; iii: data repositories to capture and process this data and make it available to the wider research community; and iv: computational microbiology expertise (high-precision SNP calling, assembly and genome binning, numerical ecology, host-ecosystem interaction modelling, entailing multi-modal analyses, such as multi-omic and network analyses, coupled to visualisation tools and evidential frameworks) to explore the data and derive insights. The UK possesses world leading technological expertise in each of these areas. We see the challenge for the next years in finding synergies and linking the, sometimes disjunct, parts together, to enable increased exploitation.

The changing microbiome data landscape

One of the most significant drivers of microbiome research in recent years has been the falling cost of sequencing and the hugely important innovations in bioinformatics and computing. Marker gene studies for microbial community composition are particularly inexpensive and easy to use, and therefore dominate the landscape. Shotgun metagenomics, which provides much greater utility, is less widespread. However, its price is likely to follow a similar curve to genome sequencing, meaning that it will become progressively ubiquitous over time. In addition, we are increasingly seeing the uptake and value of long read sequencing, with single cell sequencing becoming more common. The application of these technologies will significantly aid the generation of single-amplified and metagenome-assembled genome libraries and contribute to our understanding of the physiology and within population variation of the collective microorganisms being studied. The ongoing roll out of portable sequencing, meanwhile, offers game-changing potential to truly democratise the technology, opening new possibilities for precision tailored medicine, nutrition, agritech, and so on, based on personalised or localised microbiome analysis.

At the same time, construction of a more complete understanding of the systems under investigation requires that we move beyond measurement of microbial DNA. Here, technologies like microfluidics and mass spectrometry come to the fore, enabling techniques such as metabolomics and metatranscriptomics to provide mechanisms to model communications between microbes and their hosts. The increasing availability of multi-modal data types, and the requirement to integrate them with sequencing data, increasingly precipitates demand for innovation in the downstream analysis technologies.

Data standards and experimental design

Microbiome studies can be limited by incomplete metadata, where sampling, measurement and contextual information are not fully captured. This is a particular issue for the repositories that aim to make microbiome data available to the scientific community, as lack of contextual information limits data reuse and utility for knowledge extraction. Community driven data standards are available for microbiome data, but work is required to ensure they are able to cope with evolving scientific developments in the field. Facilitating standards uptake and adherence is also a challenge. Open sharing of primary data (metadata, sequencing data) is often not enforced and can lead to studies being not reproducible, or limited groups of individuals leveraging their access to datasets funded by public resources. Development of mobile apps and IoT technologies, such as wearables, could potentially play a role here, through capturing and structuring appropriate data.

Equally important is the area of experimental design and setting initiatives for researchers to move beyond purely descriptive to causal study questions.

The interdisciplinary challenge

One reason for suboptimal experimental design may be a lack of awareness of potential downstream technologies and applications, with few researchers possessing expertise in the full data continuum, from data generation to multi-modal analysis. In addition, researchers may find themselves unable to access the requisite tools and techniques because of the gulf between the biological and computer science fields that represent either end of the data continuum. The development of relevant visualisation tools may act as a lingua franca, helping scientists from different disciplines communicate ideas and collaborate throughout the complete data journey, from data generation/ preprocessing, via exploration and hypothesis generation, to communication of results.

Nevertheless, the knowledge gap between biologists, computer scientists and statisticians will increasingly become an issue as multi-modal analyses come on stream, with multiple disparate networks of data to integrate and interrogate. To address this, cross-disciplinary training is required to maximise knowledge exchange between disciplines, catalyse experimental co-design, and enable researchers to access emerging technologies that are germane to the field. This also requires advances in human interface design, enabling investigators from different specialities to interact efficiently with the data. This domain is the current focus of e.g. Eagle Genomics, with the aim to enable more efficient collaboration and more effective data analytics.

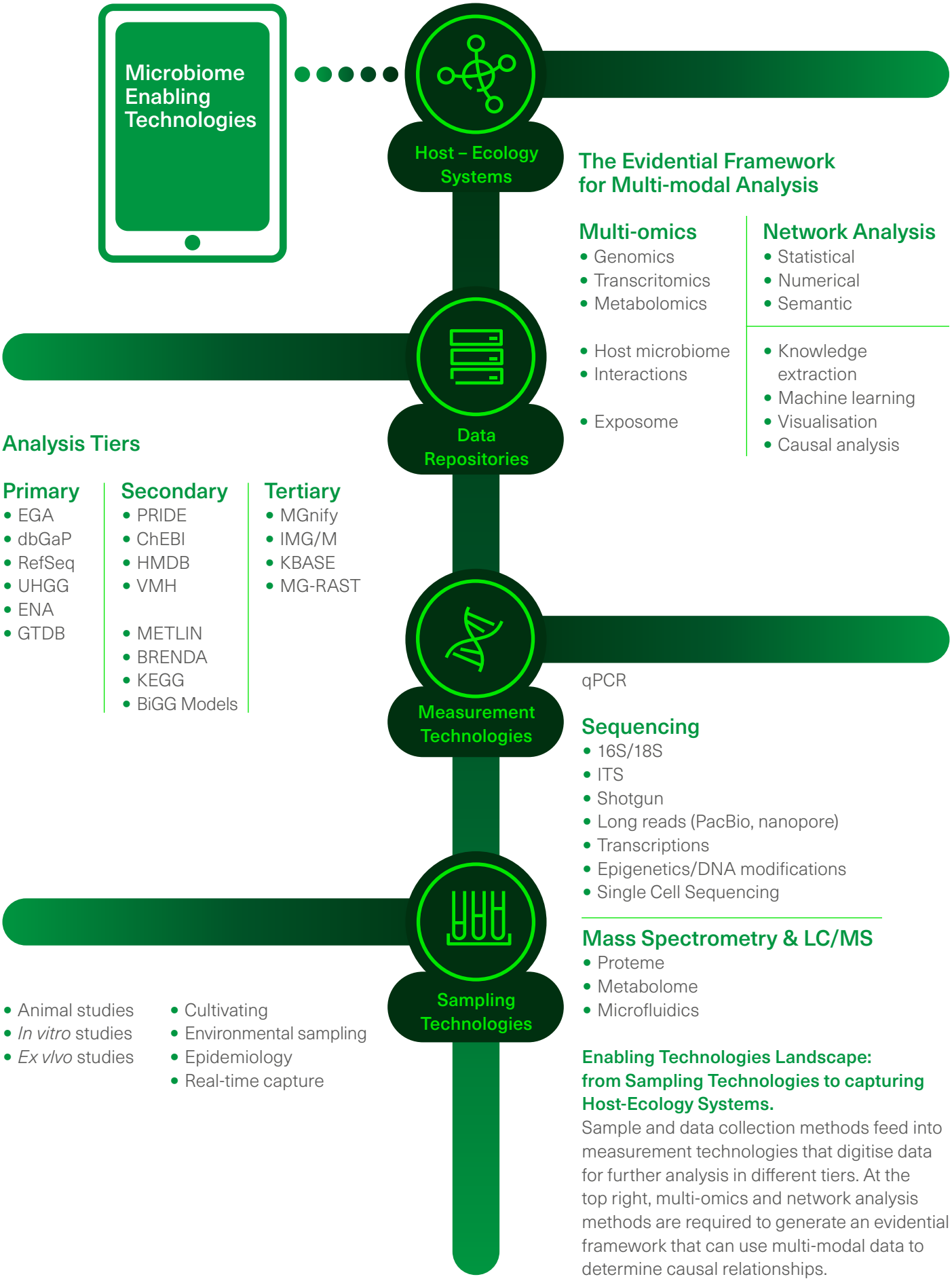
Recognising the interdisciplinary nature of the challenge, specialist microbiome focussed research institutes, such as the Quadram Institute (or virtual institutes, exemplified by the Alan Turing Institute) may be required, along the lines of the US Lawrence Berkeley National Laboratory-led National Microbiome Data Collaborative (NMDC, microbiomedata.org). This resulted in the Tri-institutional Partnership (TrIP) of microbiome institutes in the Bay Area (US), bringing together research groups and companies with relevant disparate expertise[1]. Of similar importance is the substantive funding the US National Cancer Institute (NCI) has awarded to the Center for Applied Microbiome Science in support of further development of QIIME2[2]. innovation in the downstream analysis technologies.

Integrative research funding

Finally, a clearer demarcation of which funding body is taking leadership in the microbiome area is needed. At present, many projects fall between the responsibilities of the MRC, EPSRC, NERC and BBSRC, which results in inefficiencies during the submission process and grant applications not aligned with the aims of the funding bodies. Given some of the challenges described above, specialist strategic funding sources for microbiome that enable all parties with relevant expertise to come together are necessary if we are to capitalise on the UK's technological strengths in this field.

Equally important is the area of experimental design and setting initiatives for researchers to move beyond purely descriptive to causal study questions.

1. www.newscenter.lbl.gov/2020/08/06/new-partnership-seeds-microbiome-research/
2. www.eurekalert.org/pub_releases/2020-09/nau-rr092220.php



Enabling Technologies Landscape: from Sampling Technologies to capturing Host-Ecology Systems.

Sample and data collection methods feed into measurement technologies that digitise data for further analysis in different tiers. At the top right, multi-omics and network analysis methods are required to generate an evidential framework that can use multi-modal data to determine causal relationships.

Section 11.

Diagnostics

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Section 11. Diagnostics

Microbiome Diagnostics can be defined as any diagnostic built around the presence, absence, and abundance of microbial species, genes, pathways, proteins, and/or their metabolites to improve health. This definition includes disease diagnostics, disease prognostics, and therapy outcome predictive tests. Studies have linked the microbiome to disease onset, progression, and therapy response across a range of areas, particularly chronic autoimmune and inflammatory conditions for which cures are not yet available, but also including obesity, cardiovascular disease, and cancer. As such, there is a vast scope for where microbiome diagnostics could be used in the clinic. Microbiome diagnostics could be employed to improve disease diagnostics, quantify disease risk, predict disease severity and progression, and tailor drug-choice to individual patients. Each of these applications would bring substantial health economic benefits, making microbiome diagnostics an important tool in the future of precision medicine. Microbiomes are often specific to body site, meaning diagnostic tests will encompass a range of clinical samples including, but not limited to, gut biopsies, stool, saliva, blood, vaginal swabs, and skin swabs.

The UK is in a unique position to develop microbiome diagnostics. It is home to world-leading microbiome scientists and academic centres of excellence. Across the UK, several start-up companies are working in the microbiome diagnostics space. The UK also has a national health system which allows for the development and integration of datasets from large long-term cohort studies. However, there are challenges ahead in moving the diagnostics field forward in the UK. We have identified three key areas where the UK can improve to become world-leaders in microbiome diagnostics:

1. Develop a coherent funding strategy to bring the UK microbiome field together.

2. Standardise microbiome practices to support innovation and coordination.

3. Ensure accurate communication of scientific evidence to the public.

Develop a coherent funding strategy to bring the UK microbiome field together

The UK lacks a coherent strategy for funding translational microbiome research and product development. There are no dedicated funding streams for R & D in the microbiome diagnostics space, there are few funding opportunities for translational research, and there are few opportunities for knowledge transfer between academia, industry, and healthcare. The field has become fragmented and lacks the coordination to tackle common problems such as effective standardisation and standards of reporting, both important for clinical integration. We need to establish the microbiome as a unique discipline and train scientists with the skillsets required to ask appropriate questions and generate, analyse, and interpret microbiome data accurately in order to answer these robustly. We need to provide opportunities for knowledge transfer between academia, industry, and healthcare, and ensure effective integration of these three sectors to allow for meaningful clinical studies and intelligent interrogation of microbiome-specific problems. We need to reinvigorate the field and establish partnerships to solve common issues.

Recommendation: UKRI should establish funding streams dedicated to translational microbiome research and microbiome diagnostics. A particular focus of funds should be to strengthen collaboration between academia, industry, and healthcare. This includes funding for postgraduate training of scientists, training of clinical academic fellows, retraining of existing scientists, and ensuring the growth of microbiome expertise in senior leadership positions. This funding should be microbiome-centric rather than centred on diseases where the microbiome is implicated. This recommendation will likely require a rethink of the panel and process by which funding bodies review grants.

Standardise microbiome practices to support innovation and coordination

It is important to differentiate microbiome diagnostics which measure defined analytes from diagnostics which evaluate changes in microbial taxa and composition. The former requires the production of accredited reagents and laboratories to perform biomarker discovery and run diagnostic tests. The latter requires a more comprehensive standardisation due to the variability which exists across sample collection, sample analysis, and results reporting. In both cases, access to high-quality datasets which are commutable across laboratories is needed for meaningful interpretation of results. Standardised reporting of results is fundamental to integrating microbiome science into the clinical arena in order to ensure consistency for patients and practicality and easy comprehension for clinicians. Inclusion of appropriate standards in all assays needs to be defined and followed. All the above needs to be underpinned by clearly established regulatory paths to market and routine clinical sampling and biobanking to expedite rapid diagnostic validation.

Recommendation: A network of the UK biological standards body (NIBSC), regulator (MHRA), industry, biobanks, academia, and clinicians should be established and funded to address the collective regulatory, standards, and biobanking needs of the microbiome diagnostics community.

Ensure accurate communication of scientific evidence to the public

Articles are routinely published on the microbiome which make extravagant claims. Companies have been established which claim to measure 'gut health' though the evidence behind these claims is unclear and, in some cases, unsubstantiated. Collectively, this misrepresentation undermines the credibility of both clinical and consumer-facing microbiome diagnostics and spreads misinformation to the wider public about the health benefits which microbiome diagnostics can bring. Notably, charities and other stakeholders (e.g. British Society of Gastroenterology and Guts UK) are working to educate the public and clinicians using evidence-based science. However, funding for UK-wide coordination of these efforts is urgently needed.

Recommendation: Funding should be given help to coordinate existing public engagement initiatives for the microbiome and to set-up a dedicated portal to act as a 'fact-checker' for microbiome diagnostics. This portal will serve as a source of information for patients and medical health professionals and should be overseen by an independent group of experts.

Section 12.

Intellectual Property

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Section 12. Intellectual Property

Introduction

Intellectual Property Rights (IPR) are one of the range of tools available to businesses in the microbiome field for optimising a return on investment in R&D and in reputational growth. Like any tool, they can only optimise the benefit to your business if you have a commercially relevant strategy for employing the correct choice of available IPR tools in the correct manner within the context of your business.

What Can be Protected by IPRs?

Patent Rights:

A granted patent provides a 20-year monopoly for your invention. To be valid, the invention must be new, inventive (i.e. not obvious, normally requiring the demonstration of a surprising technical advantage) and sufficiently disclosed so that others can work the invention based on that information provided in the patent application. The microbiome field is constantly developing a hugely diverse range of technological innovations. These can be product innovations (such as personal care, food, agricultural or therapeutic compositions) or process-innovations (such as methods of diagnosis, cryopreservation, species/strain analysis or manufacture of any of the aforementioned products). If the aforementioned criteria are satisfied, all such classes of invention may be protectable by patent rights, for example:

- A new microorganism; either previously unidentified and in a form isolated from its natural environment, or modified (e.g. genetically).*
- A previously unidentified extract from a microorganism.*
- A new consortium of known and/or unknown microorganisms.*
- A new composition of matter including known microorganisms/extracts and/or any of the above. For example, cosmetic, food or therapeutic formulations for administration of microorganism or extracts.*
- A new therapeutic use of known microorganisms/ extracts or any of * (e.g. use in treating a new disease, or patient group, or new dosing regimen).
- A new method of using a known microorganisms/ extracts or any of * defined by novel steps, or novel order of known steps.
- A new method of culturing a microorganism or generation of extract therefrom.
- A diagnostic method based on analysis of the presence/ absence/proportion of microorganism populations.

Those classes of invention marked* must be sufficiently characterised such that some form of utility can be demonstrated, although the claimed invention does not have to be restricted to that use (and so can provide claims of the greatest possible breadth of protection, e.g. patented claims drawn to the first listed invention could prevent others from any use of the claimed microorganism). The later inventions are characterised by use and so are restricted to that claimed only in the context of the use recited in the claims of the patent.

Diagnostics, where the invention rests in bioinformatics (e.g. computing power reduction when matching microbiome sequences for identification; or preserving ratios of microbes in the sample when processing microbiome reads, known as a sequencing library), have proven historically more challenging to patent than other diagnostic inventions (e.g. those based on the simple detecting presence/absence of a microbiome-biomarker). This is less the case now, if the technical result to be achieved by the bioinformatic-analyses is clearly described.

All the above generally holds true for most national patent systems, with the notable exception of the US. The only form of new microorganism that is patentable in the US are those that are modified. For this reason, for un-modified microorganisms, strategies focusing on formulations or use-restricted claims are important. The only consortia that are patentable in the US are those that demonstrate synergy from the combination. Obtaining commercially important broad patent claims for almost all forms of diagnostics in the US has become challenging, and a constantly evolving target. To optimise likelihood of success, one should take a proactive approach; starting up a dialogue with the US examiner in charge of the case is normally essential.

Know-How: Know-how is the knowledge of your business and its practices that you keep confidential, and has value for your business because of that confidentiality. It can relate to technical information, data, trade secrets, SOPs etc. A confidential key step in a culture method that cannot be guessed at from the product may be protected by know-how. Unlike patent rights, know-how cannot be used to prevent someone from using that step if they identify it independently.

Design Rights (registered/unregistered): Provides protection for novel features of the appearance of products. Potentially relevant for those developing physical products such as diagnostic devices, samplers/applicators or culture equipment.

Copyright: Provides the owner with exclusivity for copying literary and other creative work. This relates to manuals and other written materials, but also software. Whilst this may be useful for protecting bioinformatics-related work, patent protection can provide broader protection as it aims to protect the underlying idea not the specific code.

Trade Marks: Trade Marks can be used to prevent others from using names or logos that are confusingly similar to those that you use in relation to activities of your company and/or its products/services. Essentially, trade marks protect the link that you develop between those names/logos and the reputational value of your business.

Developing an IPR-strategy

An IPR strategy aims, by the strategic selection of IPRs, to build an "exclusivity cloud" that defines a space in the market that corresponds to at least the commercial focus of your business and that is difficult for others to enter. Clearly, this can be a powerful tool for competing in the market with a unique product/service, but such an exclusivity cloud can also help to raise investment, elevate the net value of your business and assist in deal making with collaborators or competitors. When such tools are not chosen in a strategic way, or simply "left in the shed" without being used, they can represent a significant drain on resources that can likely be put to better use elsewhere.

Selecting IPRs strategically requires an understanding of what is protectable by which types of IPR, the breadth of protection and associated cost, and the value of protecting the relevant part of the cloud to the business. Patents normally provide the greatest breadth of protection for microbiome innovators, but are the most expensive to secure. Patent protecting only those aspects of the company's innovation that drive the most commercially relevant unique offering is often a financial imperative for microbiome SMEs. Such a company should then look to other forms of IPR to help efficiently and densely back the cloud with IPRs. Technical innovations not selected for patenting can be considered for protecting by know-how; particularly relevant for innovations that are not "reverse-engineerable". Such an assessment for single products of high value (e.g. therapeutics) will often justify a strategy seeking numerous patent rights. It can be more challenging if a wide range of lower-value products are in development; each product alone not justifying the expense of a patent (as you may find in some ranges of food or cosmetics products). In such situations, it may be advisable to identify a single technical innovation that runs through all products in the range, and focus protection of that innovation in a single patent. In some parts of the industry, it is not practical to attract customers by shouting loudly about technical advantages, particularly if those advantages are therapeutic and the product is an OTC food/cosmetic/wellbeing product. Creation of a trusted and recognised brand is therefore highly important, and so trade marks may be proportionally a more important part of the cloud.

Timing for filing the registered rights (i.e. patent, design and trade marks), or of layers of registered rights, must also be part of a robust strategy.

The normal window for filing of registered design would be after "design freeze" and associated with the timing of product launch. As a rough guide, Trade Marks should be filed before the business has invested sufficiently in the brand that they would not wish to start again with a new brand. However, filing, or at least seeking advice, as early as financially possible is sensible as it can provide an early indication of problems with registrability and ensure prior rights over competitors/trolls.

In the case of patents, the later you file, the greater the danger the invention becomes known and can no longer be novel. However, with more time comes a greater understanding and evidence for the invention, and so a broader scope of protection is likely to be achievable. This therefore requires a balanced assessment, perhaps clearly shown when considering how to define your microorganism in patent claims. Taking bacterial-innovations as an example, bacteria must be clearly defined in claims so that the public can understand if a given bacterium falls within the scope of that claimed. Additionally, selecting to define that group in the manner presented in the claims must be justified by provided evidence that it is reasonable to expect the members of that group to operate in the manner required by the invention. On first characterising a new bacterial strain, one can clearly and sufficiently define that strain in a claim by reference to a deposit made under the Budapest Treaty. This likely narrowly restricts your invention to the bacterial strain "on your bench". Whilst in some instances this may be enough, in others broader protection may be required to keep competitors out of the cloud. One can therefore seek to direct claims to a broader class of bacteria, e.g. by defining a group of bacteria that share a familial relationship with the bacteria empirically demonstrated to have the required utility. For example, by directing claims to the species (maybe even genus) of the identified bacterial strain, or with reference to those having a defined sequence homology to a gene of that strain (e.g. 16s). One stands a better chance of obtaining such broader claim language if you can provide evidence that other strains within your definition share the phenotype required by the invention; this of course requires lab-time. There are weaknesses associated with each way of defining bacteria by familial relationship, and so multiple alternative definitions of this sort are often included in a single patent application. The value of such claims should not however be underestimated; such claims have sustained challenges by competitors and companies have raised many millions of dollars based on IP estates with such claims. Ultimately, however, the greatest breadth of protection is likely to be secured if one understands the structural origin of the function on which the invention is based. For example, if one can define the bacteria as one including the gene that provides function, one has the potential to capture a vast array of bacteria, including potentially synthetic constructs that may be very different to the originally identified strain. Finally, optimum value of an IPR strategy can only be achieved if it is integrated into the wider strategies of your business. Whilst this includes an appreciation of IP spend and expected cash flow of the business over time, wider considerations may be of value. For example, IP prosecution strategies can be timed (to an extent) to provide "good news" that coincide with key milestones for seeking investment. Pre-clinical and clinical studies can provide data that significantly improve the robustness of patent filings, if the timings for each can be co-ordinated.

Identifying Potential High Value IPR space

Whilst development work is normally driven principally by the science coming out of the lab, there can be value in identifying and focusing on developments in relatively IPR free-space in relation to potential emerging areas of commercial significance.

Potential examples are:

- Clinical disorders that are of growing commercial focus but underrepresented in the patent literature (e.g. therapeutics directed to lung disorders).

- We are likely to start to see waves of approvals for microbiome-based therapeutic products. Any formulation or manufacturing technology that can de-risk therapeutic developments will likely be embraced by regulators and fuel faster approvals when the new technology is applied to the therapeutic products applying for approval. If such technology is generally applicable, it may be attractive for licensing to a large range of companies developing different therapeutic products, and may on that basis be more valuable than each product individually.

- Conventional small-molecule therapeutics on the market have a clear and defined value to their proprietors. Such proprietors can therefore relatively accurately define their loss when the exclusivity period for their product ends, a considerable sum if the product is a blockbuster. Microbiome-adjuvant technology can, in certain situations, be a tool used to essentially extend the exclusivity period for that product (e.g. check-point inhibitor adjuvant technologies). By associating your microbiome developments with a blockbuster approaching an end to their exclusivity period, could result in a technology with a clear customer with significant funds.

Collaborations and MTAs

A Material Transfer Agreement ("MTA") is a contract governing the transfer of materials and is a means of protecting any company's research and commercial interests in its valuable property. The range of materials transferred under MTAs may be diverse, although they generally fall within the biological/chemical category. Clearly, for the microbiome field, bacterial cultures, bacteriophage, and bacterial-extracts may form the subject of an MTA. The materials (including any accompanying information concerning structure, morphology, production or use) may hold value through existing patent or other IP protection or simply represent valuable sensitive and confidential information which, having been developed by your company, you would not want to be used by a third party (or any competitor) without the appropriate restrictions in place to protect the company's interests and investment. This value may not always be evident at the time of transfer – the materials or information could represent a key precursor to your company's future projects, a component for other projects, or, it may be the information generated from the evaluation of your materials that represents the value. It is therefore only natural that any successful and experienced biotech company will have a clear process in place to ensure any transfer and use of its assets are governed and protected in the appropriate way using well drafted MTAs and a clear structure of oversight tracking which materials have been transferred where and which materials have been transferred into the company from third parties. Without this any company risks unnecessarily passing over or loosing control over its valuable assets or, at the very least, creating an element of uncertainty over what is rightly owned by the company. No company wants to waste time and energy litigating over what it rightfully owns simply due to fact it has not implemented the appropriate contractual terms and has not taken the time to ensure it has a clear and embedded process of oversight. MTAs can require a level of negotiation, quite often due to the fact they will include a number of restrictive provisions on the third party – but, for the reasons outlined above any successful biotech company will accept this is a small pain to bear compared to the consequences of not having the protections in place. The use of a good company MTA template and an embedded clear process for teams to follow will often very quickly create a more streamlined and professional approach and negotiation time will inevitably reduce with experience.

Where your company is supplying materials and information to another organisation (Recipient), there may be a variety of reasons why you would consider a written MTA to be essential. In particular, you may wish to have a legally-binding contract in place to ensure that your company has some or all of the following rights:

- **Permitted use of materials:** to control or limit the use that the Recipient is permitted to make of the materials in research.
- **Prohibited use of materials:** to prohibit the Recipient from using the materials for non-research purposes, e.g. using the provider's engineered bacteria to produce a therapeutic peptide for sale to third parties. (If the provider is willing to allow this activity, it should generally be under a separate licence agreement rather than an MTA.).
- **Access to results:** to obtain access to any results and data obtained from the Recipient's use of the materials.
- **Confidentiality:** to prevent public disclosure of the company's confidential information.
- **Publications:** to ensure that the company is given appropriate recognition (or direct involvement, e.g. as a co-author) in any publication of those results.
- **Use of results:** to obtain a legal right (e.g. a licence or option to take a licence) to use or own those results and data (e.g. in further research or commercialisation – this is often a core requirement for any commercial provider).
- **Ownership of resulting IP:** to obtain ownership rights in respect of (some or all of) those results and any patents or other intellectual property generated from them.
- **Royalties, etc:** to receive a share of any commercial revenues (e.g. licensing income) generated by the Recipient through use of inventions made using the materials (this is again often a priority for any commercial provider).

GDPR Implications

The intellectual property rights which protect commercial data will also protect information which qualifies as "personal data" under the GDPR. The breadth and depth of what qualifies as personal data has been broadened and deepened by the Court of Justice of the European Union's jurisprudence since the 1995 Data Protection Directive came into being. In so far as any information which relates to a living individual is capable of being attributed to them (even indirectly or bycombination with other information which may be in the hands of a third party) or is capable of being used to distinguish that individual uniquely (without ever knowing their "real-world" identity) it qualifies for the protections afforded by the GDPR. In the context of microbiome technologies, thiscould for example be information relating to profiling of the gut-microbiome of an individual, or data uploaded by a vendor of an App-based tool from their customers using the App. These protections extend to data which already benefit from the application of a code unless the key has been destroyed. Thus, data derived from analysis of and linked to samples labelled with indirect identifiers fall in-scope of the GDPR.

Therefore, MTAs and Data Sharing Agreements should deal with the following GDPR-implications and assign responsibility and liability for compliance clearly. This is particularly important where collaborations between third parties may mean they qualify as "joint controllers" in GDPR parlance. Without agreements setting out each party's role and responsibilities one (innocent) organisation which is jointly determining the "how" and "why" personal data are processed may end up being legally and financially liable for their collaborator's missteps.

The permissions which the donor attached to their sample and/or data should be clearly recorded and scrutinised to ensure any proposed use is consistent with those permissions. Compatible and not inconsistent re-use may be permissible, including under the GDPR's "Research Purposes", but careful due diligence should be undertaken and advice sought before seeking to re-purpose samples and/or re-use coded personal data for purposes which are potentially secondary to those about which the donor was informed. This is particularly important when processing biometric, genetic and/or health information because these categories of personal data qualify as "special category personal data" and therefore benefit from stringent protections under the GDPR. Amongst these GDPR protections are the international transfer restrictions placed upon proposed transfers of coded personal data out of the UK/EU to non-EEA countries which do not offer levels of protection equivalent to those offered by the GDPR. Following an expansive decision handed down by the CJEU in July 2020 on this topic, such transfers should be subject to particular due diligence and highly regulated by contract. The GDPR imposes a specific obligation that as soon as directly identifiable personal data are no longer required in such format they should be pseudonymised. This pseudonymisation does not render them "anonymous" in the eyes of the GDPR and so does not take them out of scope – rather the GDPR conceives of this coding as a necessary protective measure which mitigates data privacy risk, but it does not render the GDPR inapplicable.

With the end of the UK's "Transitional Period" on 31st December 2020 the EU's GDPR will cease to be applicable to UK based organisations' processing of personal data which will instead by governed by an equivalent Act of Parliament called the "UK GDPR". While the two versions of the GDPR will be identical as at the 1st of January 2021, in time where the regulators and/or the applicable courts begin to issue diverging opinions managing the transfer of materials and/or data between the UK and the EU 27 will become more complex with a likely increase in the time and resources necessary to negotiate what may currently be fairly routine MTAs or DSAs. A further complicating factor is that under the deal pursuant to which the UK left the EU, the UK Government agreed that any personal data controlled by UK-based companies (which was originally collected when the UK was part of the EU) will continue to be processed in accordance with the EU GDPR as from 1st January; thereby potentially obliging UK-based controllers to run two separate data protection compliance regimes over a database used for just one purpose/project.

The "one database two data protection regimes" conundrum may be exacerbated because the EU GDPR gives each of the remaining EU 27 member states the power to legislate further in their local laws on how biometric, genetic and heath data should be processed. If the member states take advantage of this power the number of laws governing one database could potentially multiply beyond the two legal regimes we already know will exist as at 1st January 2021.

This confused and confusing picture is the subject of an EU Joint Action Working Group which is seeking to arrive at an EU-wide approach, possibly to include a Code of Conduct on the "Research Purposes", which would be welcomed. Until that level of clarity is achieved (anticipated to be years away) companies are well advised to revise their standard MTAs, DSAs, due diligence policies and procedures to make sure that they are going to be able to use the samples and data they acquire for the purpose they anticipate and are not subsequently unintentionally blocked by falling foul of the high level of prescription laid down in the EU GDPR, the UK GDPR and/or the EU 27 member states' local laws on handling biometric, genetic or health data.

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