Evidence regarding the scientific understanding of the impact of the gut microbiome on health and microbiome-based interventions that can be incorporated into healthcare programmes

Dr Marina Ezcurra, Senior Lecturer in the Biology of Ageing at the University of Kent
for The All-Party Parliamentary Group on the Human Microbiome

My expertise and role in the research community

I am biogerontologist with expertise in the fundamental biological processes driving ageing, and how these processes are altered by the gut microbiome. **As we are uncovering the mechanisms of these interactions, microbiome science will offer avenues to target processes that drive ageing and thereby prevent age-related diseases and promote lifelong health.** In addition to leading a research group at Kent, my expertise within the research community has led me to work with policy makers; I gave written and oral evidence to the House of Lords Science and Technology Committee, providing policy makers with input on new strategies for the UK's ageing population. I write articles for the media and charities (The Conversation, Open Access Government, Society for Applied Microbiology); give expert comments (New Scientist, The Express, Patient); and my research has featured in newspapers articles (e.g. The Daily Telegraph) and world leading popular scientific journals (e.g. Science). I am a trustee of the British Society of Research on Ageing (BSRA) and play an important role in supporting UK ageing research community and engaging with stakeholders (charities, policy makers) and the wider public. I regularly peer-review grant applications scientific manuscripts on the microbiome and ageing for multiple funding bodies and journals. I have been awarded research grants to research the microbiome from multiple funding bodies (BBSRC, Innovate UK, Wellcome Trust, Royal Society, National Biofilms Innovation Centre).

Background

Technical advancements of high-throughput sequencing and metagenomic tools have enabled new insights to microbiome function, including a bidirectional relationship between the microbiome and host physiology. It is now understood that the gut microbiome is an important link between nutrition, metabolism and health. Microorganisms catabolise nutritional substrates present in our food and produce a vast range of metabolites such as short chain fatty acids, amino acids, bile acids, vitamins and neurotransmitters - these microbial metabolites affect host physiology and susceptibility to disease by altering metabolism, immune function and neurological function. Changes in the composition of the gut microbiome have been implicated a wide range of diseases and health states. The recent development of sequencing techniques has enabled profiling of microbiomes in humans and resulted in an explosion of studies demonstrating associations between the composition of our microbiome and many different diseases. Some of these links are not surprising (intestinal infections, inflammatory bowel diseases), whereas others are less expected (obesity, cardiovascular disease, cancer) or completely unexpected (major

depression, neurodegenerative diseases, autism spectrum disorders)[1–3]. **Mechanistic studies in model organisms and interventional studies in humans are starting to uncover how the microbiome can be utilised to develop therapeutics and interventions to prevent disease.**

Q1. In the field of the gut microbiome, health and disease, which areas of gut microbiota research have the strongest evidence for benefits?

Strongest evidence for microbiome effects on health and potential for microbiome-interventions

Protection against intestinal infections
The most striking example of diseases with well-established and direct links to the microbiome and for which microbiome-based treatments are being used is reoccurring intestinal infections with the bacteria *C. difficile*. *C. difficile* infections are characterised by severe diarrhoea, causing 15,000 deaths a year in the United States alone. The first-line treatment for *C. difficile* infections is antibiotics, which wipes out *C. difficile* but also a large part of the healthy microbiome. Antibiotics leave the patients susceptible to new infections as *C. difficile* can easily establish itself in absence of a healthy microbiome, and about 20% of patients have reoccurring *C. difficile* infections. Faecal microbiota transplants are now becoming accepted as an effective treatment. Controlled trials of faecal transplants, in which stool from a healthy donor is transplanted to help re-establish a healthy microbiota, have reported over 90% efficacy in clearing reoccurring *C. difficile* infections. Due to the complexity and variability in donor stools, combined with a limited understanding of the ecological forces that shape the microbiota, faecal transplants are not free of risk for the receiver. For these reasons, next-generation microbiota-based medicines will likely become the preferred option. As we learn more about how the microbiome protects the host against pathogenic infections, defined interventions with rationally selected mixtures of microorganisms or their products that can be more reliably managed will be used[4,5].

Metabolic syndrome
Observational findings achieved during the past two decades suggest that the intestinal microbiota affects the metabolic health of the human host and contributes to metabolic diseases such as obesity, type 2 diabetes, cardiovascular disease and cancer. The microbiomes of obese and lean people differ in striking ways; obesity, insulin resistance and fatty liver disease are associated with less microbial diversity and higher levels of particular bacterial groups e.g. *Firmicutes*. Interventions that induce weight loss and improve metabolic functions in both animals and humans result in shifts in microbiota composition, indicating that the microbiome plays a role in metabolic disorder. To gain a mechanistic understanding of how the gut microbiota affects host metabolism, microbiome research is moving from descriptive microbiome profiling to cause-and-effect studies. For example, faecal transfer of microbiotas from obese human donors to germ-free mice induces weight gain and recapitulates of the metabolic phenotype the donors in the animals[6,7]. Joint analyses of high-throughput human multi-omics data, including metagenomics and metabolomics data, together with measures of host physiology and mechanistic

experiments in humans, animals and cells hold potential as initial steps in the identification of potential molecular mechanisms behind reported associations.

Brain and nervous system disorders

For some diseases associated with the microbiome it can be challenging to envision causative links at first, such as autism spectrum disorder, major depression and neurodegenerative diseases. However, the gastrointestinal tract and the brain are physically and chemically connected to each other. The vagus nerve directly connects the gut with the brain, providing a means of neuronal transmission between these two organs. In addition, gut microbes produce chemical compounds, including neurotransmitters that directly affect neuronal activity, metabolites with neuroactive properties and other molecules that can be transported through the circulation and reach the brain and other organs[8]. Considering that a direct bidirectional crosstalk between the brain and the gut has been demonstrated, with reciprocal influence on each other's physiology and function, it is not surprising that microbiome composition can affect brain health and brain function.

There is evidence, although preliminary and mostly from animal models, for a role for the microbiome in neuropsychiatric conditions, including major depression, autism spectrum disorder, schizophrenia and neurodegenerative diseases such Parkinson's and Alzheimer's diseases. Animal models allow controlled experiments such as generating germ-free animals and performing faecal transplants. These kinds of experiments have demonstrated that gut microbes and the molecules they produce can promote or inhibit brain and nervous system disorders[2,9]. The crosstalk between the gut microbiome and the brain is a complex network of interactions that we are now starting to understand.

Q2. Do you know of any examples where gut microbiome research is currently informing mainstream health practice?
(Please explain them and comment on how widespread use is, if the interventions are considered to be successful (promising) and how you think these practices might be further improved.)

Gut microbiome-based treatments for disease are not currently used in mainstream healthcare. In the US there are private clinics that offer microbiome profiling and dietary/lifestyle advice based on profiles but this is very exclusive and mostly not evidence-based. Clinical trials for a wide range of diseases are being run by pharmaceutical companies as well as academic institutions, mostly in the US. In the UK the Microbiome Research Centre at University of Birmingham brings together clinicians and scientists in microbiology and gastroenterology to offer faecal microbiota transplants the treatment of patients with recurrent and refractory *Clostridium difficile* infection and to run clinical trials, but numbers are small and the activity is largely research-based.

Q3. Giving reasons for your answer, are there illnesses and conditions where gut microbiome science supports the integration of knowledge into healthcare programmes and treatments now?

As microbial dysbiosis is associated with a wide variety of human diseases, various strategies are now being applied to restore the native microbiota for efficient disease management. This is largely happening in the form of scientific studies involving microbiologists and microbiome researchers working with clinicians. **Microbiome therapeutics have a major potential but there is currently a massive gap between the mechanistic understanding being generated in laboratory settings and interventions that have been demonstrated to be safe and improve health in humans. There is more work to do before microbiome-based healthcare solutions can be offered widely.**

Q4. What are the specific illnesses and conditions for which microbiome science is likely to become sufficient over the next 12-36 months to support incorporation of this knowledge into mainstream healthcare?

Microbiome research is a new field that will be generating innovative health interventions over the coming years rather than months. Despite the therapeutic and economical potential, microbiome therapeutics is still in the developing stage and is facing various technical and administrative issues. More experimental trials need to be done to provide efficacy in the microbiome therapeutics through the study of the interaction between therapeutics and the host: this includes defining molecular mechanisms and in parallel conducting clinical trials in human populations.
As discussed above, treatment of reoccurring *C. difficile* infections with faecal microbiota transplantation is furthest along in terms of adopted as a treatment method. The main goal with this treatment method is to establish a stable and resilient microbiota in the patient that acts as protection against *C. difficile*. A search of registered clinical trials retrieved from the ClinicalTrials.gov database shows that by far most clinical trials using FMT target *C. difficile* infections. However FMT presents many challenges in terms of transfer of pathogens, requiring specific expertise and facilities, preventing FMT from becoming mainstream[1].

Other diseases that have been studied more extensively in clinical trials include IBS, Crohn's disease, non-alcoholic liver disease, obesity and diabetes. For these diseases the results are more varied than for *C. difficile* infections, due to the more complex role of microbiota in the diseases, and where more complex interactions with host metabolism and immunity are required to achieve the desired outcome. This complexity requires a deeper understanding of the underlying mechanisms and more targeted interventions, such as genetically engineered bacterial species or bacterially derived compounds and proteins[10]. New healthcare treatments are unlikely to emerge over the coming year.

Q5. What do you believe to be the most promising illnesses and conditions that microbiome science currently suggests might improve health outcomes significantly and/or potentially result in large financial savings, but which is still some way off and needs investment to expand the evidence base before it is ready for health care use?

This is a critical time in microbiome science; we are starting to understand and apply this science to cure and *prevent* diseases. There are now emerging opportunities for intervention in specific diseases through microbiome modulation.

Establishing healthy microbiomes for lifelong health
Microbiome science has shown that microbiomes that are taxonomically diverse and resilient against perturbations are associated with health. In contrast, decreased diversity and unbalanced microbiomes (dysbiosis) are associated with chronic diseases, obesity, and ageing. Mechanistic evidence points towards abnormal microbiomes damaging the gut barrier that keeps toxins and pathogens from crossing into the bloodstream. When this occurs, it can set off a cascade of inflammation, contributing to insulin resistance and cardiovascular, inflammatory, autoimmune and neurological conditions, as well as contribute to biological ageing. In contrast, diverse microbiomes protect and maintain the gut barrier, contributing to low inflammation and beneficial metabolism[11,12]. **The implication is that the microbiome alters fundamental biological processes related to ill-health and ageing and that we can prevent/reverse diseases through the microbiome.** Future healthcare solutions will include microbiome-based therapies targeting specific diseases as well as interventions to maintain healthy microbiomes across the life course and prevent ill-health.

Using mechanistic evidence to tailor new therapies and prevention schemes
Diet plays a crucial role in how the microbiota affects health. For example, gut microbes digest dietary fibre and produce short-chain fatty acids as a by-product, which interact with the immune system to prevent inflammation and strengthen the gut barrier. Short-chain fatty acids can also enter the circulation and have effects beyond the gut and have been implicated in important gut-brain communication affecting mental health and brain diseases. In the absence of dietary fibre, less short-chain fatty acids are produced, contributing to a leaky gut barrier and inflammatory responses that drive a wide range of diseases. Thus short-chain fatty acids have high potential to be developed into microbiome-based therapies and are being tested in many clinical trials for diseases such as obesity, type 2 diabetes and hypertension[11,12]. There is a large amount of activity in this field to understand the molecular basis and develop therapies as well as preventative strategies. Inexpensive dietary interventions can also be developed to modulate and improve the microbiota and are being tested in clinical trials.

Obesity and metabolic disease
Metabolic disease is at the forefront of development of microbiome-based therapies. As the microbiome is an important player in the interactions between diet and host metabolism. As mentioned above, short-chain fatty acids such as butyrate are likely to be developed into therapeutics. Another example of possible is the bacterium *Akkermansia mucinphilia*, a common coloniser in the intestinal mucus layer in humans that protects against inflammation and promotes metabolic homeostasis and gut barrier function. *Akkermansia mucinphilia* is currently being evaluated in clinical trials for glucose-lowering and weight-loss effects[6,13].

Cancer

The gut microbiota has been implicated in cancer and shown to modulate the efficacy of anticancer treatment. Resistance to chemotherapy or immune checkpoint inhibitors is associated with an altered gut microbiome profile and in the future modulating the microbiota could be used to potentiate cancer treatments. A number of preclinical and clinical studies suggest the use of tumour-associated bacteria can be used as diagnostic markers for cancer[10,14].

Brain disorders

A growing amount of evidence from animal models shows a role for the microbiome in neuropsychiatric conditions, including major depression, autism spectrum disorder, schizophrenia and neurodegenerative diseases such Parkinson's and Alzheimer's diseases[2]. The use of animal models to perform experiments in germ-free animals and faecal transplants have demonstrated that gut microbes and the molecules they produce can promote or inhibit brain and nervous system disorders. Proving a causative relationship between gut microbes and mental health has been revolutionary for the field of neuroscience, and clinical trials based on microbiome interventions to target brain disorders such as major depression, autism and Parkinson's are increasing. These trials include prebiotics, probiotic interventions and faecal microbial transfer. There is also increasing evidence for diet playing a prominent role in mental health and future studies will determine the extent to which that dietary interventions act through the microbiota[9,11]

Outlook

It is an exciting time for microbiome research. New breakthroughs over the coming years will lead to microbiome-based therapies and prevention schemes with major potential to improve health across the population. An increasing amount of evidence suggests the microbiome plays an important role in how we age, and can be utilised to prevent age-related diseases[11,12]. Investments from the private sector into this space have increased steadily for the last years, and there is large commercial interest; within the ageing population in the UK there is a growing demand for products and services that improve age-related health[15]. **The UK can position itself as a global leader in this sector and support the Government policy on healthy ageing and strategy to become a hub of discovery science and innovation. To achieve this, targeted and consistent investment from public and private sectors is needed, as well as coordination of researchers in industry and academia, investors, healthcare providers and policy makers. More basic research, clinical trials and investments are needed rapidly translate research discoveries into medical advances.**

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