# What Lies Within

Will unlocking the secrets of the microbiome yield a promising new horizon for medicine?

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## A World Within

*Trillions of microorganisms thrive inside us all. Their combined interactions with human biology (and the food and medicines we consume) no doubt hold further secrets – and we must dive deep to exploit them.*

The term "microbiome" was coined by Joshua Lederberg in 2001. Since then, extensive studies have sought to more concretely describe the microbiome and understand what role it plays in human health. The microbiome is defined as all the bacteria, viruses, fungi, archaea, and eukaryotes that inhabit the human body (1). There are literally trillions of microbial cells in our bodies with the majority being found in the human gut (gut microbiota alone weigh almost 2 kg in total (2)). Researchers have only been able to measure the communities of microbiota existing in humans since the early 2000s, thanks to the entry of next-generations sequencing technologies. And, as analytical technologies continue to improve, we are learning more and more – and the possibilities are exciting.

We now know that our bodies' bacteria play a hugely important role in health, including body weight, metabolism, and the immune system. There are also links with disease; for example, gut microbiota have been found to differ in individuals with diabetes. Indeed, in type 2 diabetes, gut microbiome composition is distinctive enough to be more predictive of the disease state than BMI (3).

If the pharma industry could learn to harness our bodies' natural microbial flora to improve health and treat disease, it would open up an entirely new avenue of medicine to that of traditional small- and large-molecules. Not only may it be possible to develop new treatments for diseases, such as diabetes, but it may also be possible to prevent them from ever developing in the first place. Imagine being able to target the microbiome to enhance the body's immune response. How about harnessing the microbiome with combination drugs that boost efficacy or reduce harmful side effects? It will be some time before we know the true potential of microbiome medicines, but research in the field continues to accelerate – and commercial pharma companies are beginning to take notice.

The Medicine Maker is delighted to partner with Quay Pharma to bring you this fascinating collection of articles about the microbiome. On the following pages, experts explain why they are so excited about the field and identify the questions that must be answered if we are to translate microbiome research into real health outcomes.

Stephanie Sutton
*Editor, The Medicine Maker*

Stephanie Sutton


***References***

1. *E Ferranti et al., "20 Things you didn't know about the human gut microbiome," J Cardiovasc Nurs, 29, 479-481 (2014).*
2. *British Gut, "The Microbiome," (2019) .Available at https://bit.ly/2Di5TTF. Last accessed April 16, 2019.*
3. *FH Karlsson et al., "Gut metagenome in European women with normal, impaired and diabetic glucose control," Nature, 498, 99–103 (2013).*

# UNCOVERING THE MICROBIOME

**Three industry gurus discuss the huge potential presented by the microbiome field – and consider what needs to happen to make microbiome-based medicines a reality.**

*By Stephanie Sutton and Maryam Mahdi*

## How did you become fascinated by the microbiome?

*Denise Kelly:* I'm an academic and my areas of speciality are microbiology and immunology. I developed an interest in the microbiome while I was with the Rowett Institute, which subsequently merged with the University of Aberdeen in Scotland, UK. From my academic work, I formed a spin-out company, GT Biologics Ltd, one of the earliest microbiome companies in the field. I then joined Seventure Partners, which is an investment company with headquarters in Paris and led by Isabelle de Cremoux. I was fortunate to be introduced to Isabelle, as she had her own vision for the impact of the microbiome in healthcare and was one of the first movers in the investment world with her Health for Life Fund. Isabelle's fund has supported leading microbiome companies, such as Enterome, BiomX and Vedanta Bioscience, and I now work as an investment advisor on Isabelle's life science team.

*Ronnie Farquhar:* My career has always had a microbiology focus. Both my undergraduate degree and PhD were in microbiology. I've been in the biopharma industry over the course of the last 30 years and most of my career has been spent in infection research. Study of the microbiome is an extension of my previous work.

### Contributors:

**Denise Kelly, Investment Advisor at Seventure, UK.**
**Ronnie Farquhar, CEO of Artugen Therapeutics.**
**James Leigh, Head of Corporate Development, 4D Pharma.**

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When I was an undergraduate, there wasn't an awareness of the complexity of the microbiome. It was just assumed that the bacteria that colonized the gut were there strictly to aid digestion. Today we know that the microbiome is like an organ that we've been overlooking for years. Its complexity, diversity and over-arching role in human health hadn't even been dreamt of until fairly recently.

*James Leigh:* Four years ago, I joined 4D Pharma after finishing my PhD. I'd always known that the lab wasn't for me – I wanted a job that was more closely related to the business side of science and I was really interested in early stage biotech companies. 4D stood out to me during my job search and it's been very rewarding to delve into the microbiome. Back then it was difficult to envision how impactful microbiome research would be. Over the last four years, it's really evolved into something big that I think has led the pharma industry to take a bigger interest. This can be evidenced by the increasing number of collaborations between the pharma and microbiome companies, including our own with Merck Sharp & Dohme in oncology.

## What do you think have been the main turning points for the field?

*DK:* Initially, the field was led by academia and, as we've developed better insight, some major funding initiatives – many from public funding – have boosted the field. Notable projects include the US National Institutes of Health Human Microbiome Project, and the MetaHIT project, which was financed by the European Commission. Such projects really started to put the focus on what is a healthy microbiome, and from there we were able to start recognizing how it changed in important disease states; for example, how does disease influence the microbiome and how important is the microbiome in maintaining health. Today, there are many start-ups in the area and research is moving incredibly fast.

*RF:* The development of new technologies, such as next-generation sequencing and other analytical systems that provide us with detailed insight into microbiota, have really allowed the field to take off. We now know much more about the genomic makeup of a microbiome and we also have technologies that allow us to culture various components. Thanks to all of this work, the community is beginning to appreciate the interactions between the microbiome and drugs, which may boost or hinder drug efficacy. This huge step forward allows us to observe the side effects caused by these interactions – and even modulate the efficacy of drugs we're testing.

*JL:* The field has evolved from a time when many researchers were focusing on identifying taxonomical differences in the gut microbiome profiles of individuals with a disease of interest and "healthy" controls – essentially trying to understand which are present, absent, enriched, or depleted in patients with disease and rationalizing live biotherapeutic interventions accordingly. This approach has provided some early insights, but it has become clear that a deeper understanding of bacterial function and host-response is required. By creating a fuller picture of the ways in which organisms within the microbiome influence host immunity and metabolism, we are developing a comprehensive understanding of how the microbiome drives disease onset and progression and how we can intervene with new therapies.

## How could the increasing research around the microbiome affect the future of medicine and healthcare?

*DK:* Many companies are interested in advancing microbiome therapeutics, but approaches vary between them; for example, some companies are working on live biotherapeutic products, and others are looking at molecules that have been derived from bacteria. With some disease states, it has been noted that there is a loss of certain populations of bacteria in the microbiome, so one focus is on those approaches that add bacteria back to restore healthy microbiome structure. In other areas, it's not just a loss of bacteria but also a loss of function. As we understand more about the functional deficit associated with disease, we will be better able to identify molecular targets and address some of the disease mechanisms directly.

*RF:* As we move forward, we have to consider how drugs interact with the microbiome as part of future safety assessments. We, as professionals in the industry, sometimes overlook the effect that certain types of drugs could potentially have on the microbiome. We know that broad-spectrum antibiotics have a negative effect on the bacteria in our bodies – and the use of antibiotics presents a dilemma for healthcare practitioners as it can put patients at risk of secondary infections. But the effect on the microbiome isn't as obvious with other drugs, such as those used to modulate blood pressure or treat depression; we have to keep an open mind. It will be of great benefit if we are able to describe the types of interactions that occur with different drugs and interpret what that means for the patients we serve. Admittedly, this endeavor will be extraordinarily challenging.

*JL:* The gut microbiome has a far-reaching influence on a number of different host systems, such as the immune system, metabolism and central nervous system. Consequently, it has been implicated in a broad range of diseases, such as inflammatory bowel disease, cancer, asthma, and even neurodegenerative conditions such as Parkinson's disease. We're not just talking about correlative evidence either; some sophisticated experiments in germ-free animals have demonstrated that the microbiome can cause or exacerbate many of these conditions. Its potential impact on our future healthcare systems could be very significant. In the clinic, microbiome-based therapeutics have been shown to have good safety profiles and preclinical data indicates they have the potential to be at least as efficacious as many of the blockbuster products currently on the market. They may also be used to enhance the efficacy of existing drugs. Recent research has shown that the profile of the microbiome can affect the efficacy of immune checkpoint inhibitors (1,2). The microbiome and live biotherapeutics offer a way to improve existing drugs, make them available to a larger number of patients, and help transform cancer treatment.

## Why is the microbiome field seeing increased activity from the pharma industry?

*RF:* It's clear that much of human health can be influenced by the microbiome and that's probably the biggest reason why we're witnessing explosive growth and interest in the field. There is just so much to explore – and we need the pharma industry to get involved to help us commercialize the field. Though the GI tract is the most obvious place to look for interactions between the microbiome and its human host, we can't forget that the behavior of the microbial community of the gut elicits various effects in other regions of the body. The lungs, for example, are another major part of the body where crucial interactions happen with the microbiome.

*JL:* It's getting harder for pharma to ignore the microbiome space. Years ago, when microbiome research was only just finding its feet, there was a degree of skepticism from scientists in the pharma industry. I think many companies thought that delving into the uncharted waters of the microbiome was an overly risky bet. That's no longer the case, and this is reflected in the number of deals that have been announced. I think some players are still awaiting clinical data from larger studies before making a significant commitment. As these read out over the next couple of years, we're likely to see a substantial increase in deal flow.

*DK:* I'll add that some pharma companies have been interested in the field for a long time – Johnson & Johnson and Pfizer got involved in some very early deals, for example. But today there is a lot more activity. Recently, Genentech has funded a significant number of microbiome-based therapeutics, and many other big companies already have their own internal programs covering the area. With the amount of research coming out about the microbiome, there has been collective recognition from the industry that the field has a lot of potential. I don't think it's a cliché to say that we're seeing a genuine paradigm shift in healthcare and medicine.

## What are the biggest success stories so far?

*JL:* The speed with which live biotherapeutics in particular have reached the clinic has been remarkable. Whilst traditional drug products based on small-molecules or biologics often spend 5-10 years in preclinical testing, the strong safety profiles of Live Biotherapeutic Products (LBPs) has meant that we can get them to patients – and generate clinical data – much more rapidly. It's worth also noting the advances in product manufacturing, without which, this accelerated progress would not be possible.

*RF:* I think that FMT has inspired a great deal of innovation in the field to-date. Though it is extreme in nature, it has massively impacted the treatment of C. difficile infection in clinical settings, lowering the recurrence of the disease and improving patients' microbial diversity (although the downside is the complexity of the mixture and the fact that we just don't understand the full potential of transferring this from one person to another). For the next success stories, I'm waiting for the results that will come from our multiple, controlled randomized placebo trials that are underway. Those will tell us much about how far we have come.

*DK:* I'd argue that the real success story has yet to be written! However, it is exciting that there is a lot of clinical activity and regulatory approvals for first-in-human studies. For me, the real success story begins with phase III trials – and I think we can expect some in the next 18 months or so.

There are many companies looking at consumer products – and I know a lot of companies making good progress in this area. It's great that these types of products are already reaching patients.

## And what are the biggest unanswered questions?

*DK:* Speaking as a scientist and academic, the frustration for me is that we still don't really understand the functionality of the microbiome. I want to get to the point where we look at the molecules these bacteria are producing and can understand how they are affecting the host so that we can define the mechanisms of action. Understanding how these mechanisms work together will be a huge challenge for the field.

*RF:* We need to understand how microbiome-related treatments will compare with conventional therapeutic methods. We need robust clinical outcomes and we need to understand how they affect patients. If the action of microbiome therapy is too much of a "black box," it will be difficult to know how much to give the patient.

***"It's clear that much of human health can be influenced by the microbiome and that's probably the biggest reason why we're witnessing explosive growth and interest in the field."***

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## Microbiome Marvels

Throughout our evolution, we have had a constant companion – our microbiome. The distinctive physiological niches, comprised of bacteria, viruses and fungi, are widely present throughout the body's epithelial cells and epidermal surfaces. The skin, gastrointestinal tract, respiratory tree and vagina are some of the environments with high occupancy rates of these varied microbial communities.

**Meet and greet**

The uterine environment can loosely be defined as sterile in nature, so our initial introduction to the microbiome happens within the birth canal. However, placental contamination can result in an early introduction. In fact, it has been suggested that the bacteria found in the placental environment originate from the oral cavity and travel through the bloodstream where they influence the conditions of their new home. Intriguingly, oral bacteria like, Fusobacterium nucleatum (a type of bacteria associated with the development of periodontal disease) are thought to affect the onset of preterm births (1).

**Power Players**

Advances in modern medicine have left us with much to be grateful for. The development of antibiotics, the eradication of parasitic infections, and shifts in attitude toward diet have revolutionized healthcare systems across the board. In the West, however, chronic and autoimmune diseases are on the rise. It has been suggested that access to high-quality healthcare has impacted our microbiota, making it less resilient and unable to balance immune responses (2).

This microscopic army of microbes can elicit a whole of host of immune responses and is implicated in the onset of several types of cancer. On a global scale, the development of an estimated 20 percent of cancerous tumor growths are associated with microbially driven events (3). Microbial communities are thought to influence the onset and progression of cancer through a vast array of routes.

**A balancing act**

Gut microbiota are like fingerprints – each with its own unique commensal community. This diversity enables energy uptake and is also the key to understanding why some people are more susceptible to being overweight or underweight. A more diverse microbiome is linked to increased likelihood of a normal energy balance (4). Studies in mice have shown that the overall diversity and richness of the gut microbial communities in both obese and underweight mice is lower than that of well-nourished mice (4).

*References*


1. *YW Han, "Fusobacterium nucleatum: a commensal-turned pathogen," Curr. Opin. Microbiol. (2015).*
2. *YJ Huang et al., "The microbiome in allergic disease: Current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology," J. Allergy Clin. Immunol., 139, 1099-1110 (2017).*
3. *B Goodman, H Gardener, "The microbiome and cancer," J. Pathol., 244, 667-676 (2018).*
4. *KS Fluitman et al., "The intestinal microbiota, energy balance, and malnutrition: emphasis on the role of short-chain fatty acids," Expert Review of Endocrinology & Metabolism, 12, 215-226 (2017).*


*JL:* Ronnie is right; our priority needs to be the generation of solid clinical data showing the efficacy of biotherapeutics in large patient populations. I predict that we'll see the first generation of live biotherapeutics being pushed through within the next two or three years. It's an extremely exciting time for the industry. If more studies evaluating the efficacy of live biotherapeutics can be conducted, it should give us very clear evidence as to just how transformative these products will be.

### What other challenges are faced by the field?

*DK:* The biggest challenge at the moment is getting human validation, but success will breed success. Translating to humans is always a significant challenge – and there's plenty of evidence in the pharma industry of that. Developing robust pre-clinical models and humanizing animal models from both a microbiome and immunological standpoint that improve the translatability to humans will be key.

RF: I agree; we can't continue to wonder whether or not a patient will respond to a microbiome related therapy. But, even with robust therapies, the risk of treatments veering off course still looms. To stay abreast with the unexpected changes that might occur, we need excellent diagnostics that allow us to pick the patients who will respond.

We also have other challenges. There are definitely hurdles when it comes to growing microorganisms on a large scale. It can be extremely difficult to harvest, preserve and encapsulate the microbes, particularly when the contract manufacturing services required for their production are few and far between.

*JL:* The potential issues with manufacturing are dependent on the nature of the product. Companies focusing on single-strain products have a clear advantage in that it is possible to grow, characterize and deliver them with relative ease. Thus, the potency, purity and stability of these products can be tightly controlled. With other approaches, such as those involving larger numbers of strains, things are not so straightforward. I would also add that, as Denise mentioned, the importance of microbiome diagnostics is often overlooked. At 4D, we are working on MicroDx, which acts as a diagnostic to select patients who may respond best to this type of therapy.

*"The prospect of seeing advances in immuno-oncology is exciting and I think this may be one of the areas where we see microbiome products have the largest impact."*

**What advances in the field do you expect we will see in the next few years?**

*DK:* As a community, the field is already moving from descriptive analysis to functional analysis, and I think we're going to see further progress. I also expect the field to move away from the bacterial-centric approach and to instead look at the interplay with certain viruses.

Much of the information we have now is based on predictions that come from annotations of genes, but, as we learn to define products – what they are doing and how they impact on other human systems – it will open up the field in new ways. I also think there will be an increasing focus on the link between the microbiome and nutrition, which brings us to the question of not just curing and treating diseases, but perhaps preventing them by selective, healthy diets that can promote a healthy microbiome.

*RF:* There is room for exponential growth in this field and I think we're already getting a taste of what the industry could look like years from now. We know that microorganisms produce chemicals that act as signaling molecules for human cells, activating a number of important signaling pathways within our bodies. So, it isn't beyond comprehension that in a few years we may be able to modulate multiple human signaling proteins through the administration of microorganisms. It has the potential to be an amazing step forward for the industry.

In addition, improving the production of materials in a cost-effective and reliable fashion should benefit the industry in a significant way. It's not the most interesting or sexy solution but it's the one that will work. Manufacturing services are often slow to start because it is imperative that the commercial benefit of producing a particular product can be seen before investment. Slashing costs and introducing healthy competition in the service sector will help eliminate some of the biggest impediments in the industry.

*JL:* The prospect of seeing advances in immuno-oncology is exciting and I think this may be one of the areas where we see microbiome products have the largest impact. There are so many other important therapeutic areas – such as asthma – that could benefit from advances in the microbiome field. Consider the hundreds of thousands of patients who deal with conditions like neurodegenerative disease on a daily basis. There is huge demand for more effective therapies in this area. Contemporary research is showing us that we can manipulate the function of the CNS using gut bacteria and perhaps we can also find a way to treat Parkinson's and Alzheimer's diseases, which have proven elusive, to new therapies derived from traditional drug development approaches. Tackling the CNS issue is probably one of the most challenging, but exciting areas in which the microbiome field will evolve.

*References*

1. *V Gopalakrishnan et al., "Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients," Science 359 (2017).*
2. *B Routy et al, "Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors," Science 359 (2017).*

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# Making Medicines from the Microbiome

**In some respects, the development and manufacture of microbiome-based therapeutics are not that different to any other medicine, but the technical difficulties and facility considerations are definitely on a whole other level.**

*By Maireadh Pedersen and Ryan Wilson*

The diversity of the microbiome allows it to be exploited in various ways and the medicines derived from it are equally diverse: small molecules (for example, metabolites), large molecules (for example, enzymes and proteins) and native live bacterial cells are all emerging as live biotherapeutic-based research targets. Such medicines could transform the future of pharmaceutical drug discovery, but we only hold a small piece of the puzzle in our hands and there is much still to be explored. We still do not fully understand exactly how microbiota work within our bodies, or what happens when a live biotherapeutic is administered by a particular delivery route; how can we guarantee that it will be safe or elicit the effects we desire? As experts from across the industry explained on page 4, there is a huge amount of activity in this area, and companies are taking different approaches when it comes to researching the field, with some focusing on single-bacteria strain systems (where a single bacteria type is thought to have a benefit on a disease state) and others looking at consortia (where multiple bacteria work together synergistically). Some companies are also examining genetically engineered bacteria that could enhance certain functionality of bacteria naturally found within the body.

From a pharmacological standpoint, there is much that we do not understand about the microbiome. Take fecal microbiota transplant (FMT) as an example. We know that it works for certain medical indications (studies have shown that people have been cured of C. difficile by FMT), but the high bacterial diversity present within FMT treatment makes it difficult to work out precisely what is happening. Some bacteria don't rely on others around them, but others can be enhanced or suppressed by the presence of other bacteria and their metabolites. It is considered easier to work with a single strain because you can look at specific pathways and receptor processing, but fundamentally there is a series of complex biochemical cascades that take place in the microbiome and, at the moment, nobody is close to fully understanding all of these interactions. As analytical technology improves, we are discovering more and more unique human bacteria, but defining the mode of action, as well as the potential side effects associated with these bacteria as medicines, remains a major challenge. The microbiome extends beyond the gut; the skin has a microbiome too, which is of huge interest to companies working on therapeutics for eczema, psoriasis and dermatitis-type indications. But we don't understand how all these bacteria are interacting, how these interactions enable them to survive, and what this means for the human immune system. There is still so much to learn.

## Manufacturing hurdles

The dosage forms and drug delivery systems that can be used for microbiome therapeutics aren't really any different to those used for other medicinal products, such as topical creams, tablets, capsules, or powders for reconstitution. The goal with microbiome therapeutics is to deliver the viable bacterial cells to the expected site of action. The greater the quantity of viable cells delivered, the greater the chance of a therapeutic response. Using the oral route is perfectly feasible and some companies are investigating rectal, vaginal and topical delivery too. For example, the bacteria may need to reach the lower part of the intestine alive to have any effect and formulation scientists, therefore, need to devise an approach that will not only preserve the activity of the bacteria during its passage through the human body, but also throughout the various stages of pharmaceutical processing steps. This bacterial cell preservation becomes significantly more difficult as batch sizes are scaled up. For instance, many microbiome products that we have worked with are anaerobic and must be handled in strict anaerobic conditions. The materials are often concentrated into a lyophilized form to preserve the viability of bacterial cells and the secondary manufacturing processes need tight environmental controls in place to maintain cell viability. Fine tuning the processing steps with the sensitivities of the bacteria is a critical factor during manufacture and is very difficult to get right, but is feasible for small batches.

In a typical pharmaceutical GMP manufacturing facility, you strive to keep bacteria to an absolute minimum within the GMP facility to ensure products are stable and fit for human administration, but when manufacturing biotherapeuticsn the form of potentially "live" bacteria you are introducing kilograms of material that contain billions of bacterial cells per gram into manufacturing processes that are traditionally open loop systems. It is counterintuitive to the way you would operate a normal solid dosage GMP facility and you need tight controls in terms of how you introduce these materials, how you control and contain them to prevent cross-contamination and then, most importantly, how you clean the facility following manufacture and before another microbiome product can be manufactured.

Many biotech companies are used to working with containment level one, which is easy to decontaminate. Human gut bacteria are typically containment level two, which necessitates different controls, safety and hygiene concepts. Even when working with cell and gene therapies, companies will typically be working with containment level one. After using live bacteria, you need to completely clean down your facility and cleaning verification is different to that of small or large molecules because the traditional methods tend not to work with live bacteria. Air space must also be considered as you do not want multiple unusual bacteria floating around! Couple this with the usual challenges that accompany a GMP environment, and commercial manufacture starts to look like a serious challenge.

## The great unknown

Most industry experience in microbiome-based medicines is in early-stage GMP and that is also reflected in industry guidance. Though FDA guidance exists for early-stage microbiome products, there is still uncertainty about how early stage regulation and quality control will work when scaling up. Right now, many companies in the space are working with regulators to find ways forward; we've had extensive discussions with the UK's MHRA. Before more regulatory guidance can be released, we need a better understanding about how these bacteria will perform in clinical trials, and what the side effects might be. There have been cases where patients undergoing FMT for C. difficile or other conditions have experienced, for example, a change in bodyweight; it is well accepted that the gut microbiome may play a role in obesity and some companies are exploring this space.

Ultimately everybody will have different responses to changes in microbial or microbiome profiles, and we need more trials to uncover this. Even with traditional drug treatments, some people don't respond, or respond differently – and it could be linked to how the drug interacts with the human microbiome. Right now, most regulators are quite open to the idea of pharmaceutical products derived from the human microbiome – particularly as the bacteria used are naturally occurring and are usually present somewhere in or on the human body. We will still need to be cautious around the sub-strains that the community is only just beginning to identify. If there are currently only low doses of certain bacteria in the gut then what will happen if you take a dosage containing millions or billions of bacteria multiple times a day? What is the effect on your overall microbiome? How could this impact your overall health/immune response? This is just looking at harnessing our own natural strains but some companies are also working with genetically modified and adapted bacteria. Control around these types of bacteria will need to be even tighter. As we learn more about the area as a whole, regulators are only going to get stricter.

Clearly, there is a lot of work to do, but it's worth it: the potential is vast. Obvious avenues of promise include GI disorders, such as IBD, Crohn's and ulcerative colitis, where researchers know that there are links between the disease state and the gut microbiome and they are looking for a very localized response. But there are plenty of researchers working on delivering bacteria to the gut to study the overall systemic effect that certain microbes can have by modulating and harnessing the power of the individual's own immune system. For example, a number of groups are looking at the potential of the microbiome to treat brain disorders and mental health conditions. In the coming years, there will no doubt be failures in the field, but we are confident that there will also be a huge number of breakthroughs.

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# The Future Is Now

**Creating cutting-edge whole community-based products to unlock the full therapeutic potential of the gut microbiome for the benefit of patients globally.**

*With James McIlroy, Founder and President of EnteroBiotix*

## Why focus on whole community-derived therapeutics?

The human gastrointestinal tract is home to a dense and diverse ecosystem of microbial communities. These communities, their genomic potential and their repertoire of activity are known collectively as the "microbiome". In health, the gut microbiome lives in symbiosis with its co-evolved host and is known to influence almost all aspects of physiological function, such as contributing to metabolism, priming the immune system and protecting the body from harmful bacteria – a phenomenon known as colonization resistance.

The advent of powerful computational tools and technology has allowed scientists and researchers to characterize and profile the microbiome in a way that was not previously possible. To what extent these associations are causatively linked to a particular phenotype rather than merely correlation is currently an area of contention. However, in the case of infections caused by opportunistic gut-dwelling pathogens, such as C.difficile, it is widely accepted that disruption to the normal microbial equilibrium reduces colonization resistance, which in turn allows the pathogen to proliferate and cause an infection. It is thought that this microbiome-mediated model of disease and symptom development can be applied to other infections, such as those caused by other multi-drug-resistant-organisms, which are known to develop in susceptible individuals following long courses of broad spectrum antibiotics.

The most powerful and effective means to reinstate colonization resistance and to treat diseases associated with perturbations to the microbiome is to transfer bacteria from a healthy microbiome into the patient suffering from the disease. This strategy, known as Fecal Microbiota Transplantation (FMT), has been well studied and is a highly effective at treating infections caused by bacteria such as C.difficile, as well as potentially being effective in other conditions.

At EnteroBiotix, we believe in the power of using the body's own microorganisms to prevent and treat disease. In contrast to reductionist approaches that focus on distilling the essence of what is delivered through FMT to create a product that is standardized in terms of composition and function, our approach focuses on developing whole community-based products that build on the science of a therapeutic strategy that has been proven to work in patients. We believe that for some diseases, a reductionist approach may be more effective and ultimately more scalable, but for others the whole community-based approach will be the best for the foreseeable future.

## Establishing deep capabilities and a product that is being used in hospitals in just over two years

EnteroBiotx began as an idea I had when I was a 21-year old medical student. While on the wards, I recognized that there were issues with the way in which FMT was being delivered. The selection and screening of donors, processing of samples and methods of delivery all presented challenges, which also represented opportunities. I wondered if it could be possible to create other less invasive, more efficient ways to deliver the bacteria – for example, in a capsule that people can easily swallow? I also wondered if it might be possible to enhance the effectiveness of FMT in specific diseases by combining the donor-derived microbes with other substances that were rationally selected based on the underlying disordered physiological processes in the recipient.

What began as a conceptual project soon began to grow. Fast forward to today and we have raised over £2.5 million of investment, built a seasoned team and established deep operational experience and capabilities, including fully-integrated ISO-accredited microbial collection facilities and Good Manufacturing Practice (GMP)-compliant manufacturing capabilities under a license from the UK's Medicines and Healthcare Products Agency (MHRA).

We are leveraging this platform to develop and advance three core product portfolios. Our minimally manipulated microbiota product portfolio is composed of off-the-shelf and ready-to-use preparations intended for use in FMT. We are distributing our first product in this portfolio nationally and internationally on a named patient basis. Our manipulated microbiota product portfolio is initially being targeted to treat antibiotic resistant infections.

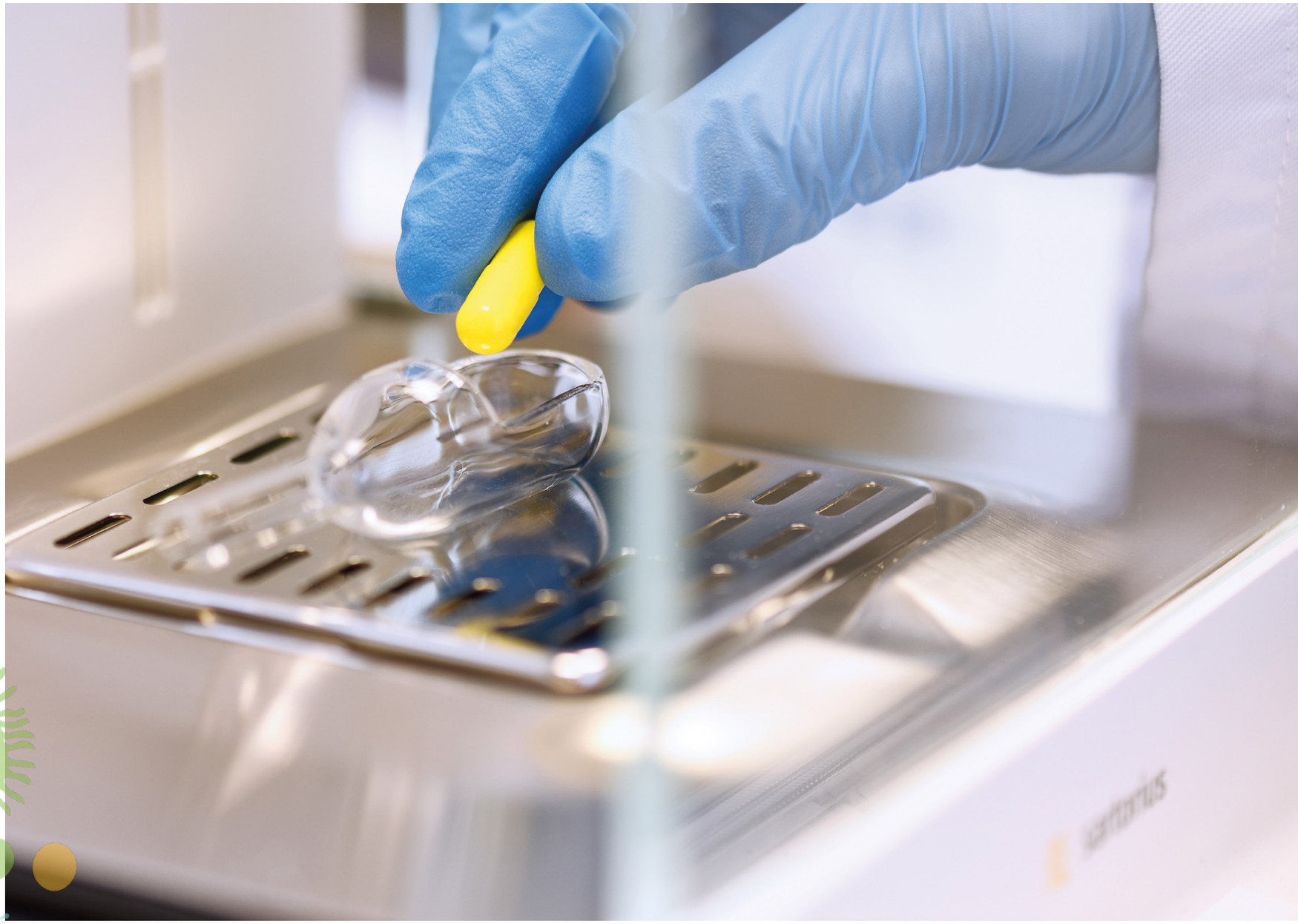
## Why target antibiotic resistant bacteria?

The medical and scientific community is becoming acutely aware of the societal and economical consequences of antibiotic resistance. As the alarm bells begin to ring louder, the traditional pharmaceutical development lifecycle can't keep up because R&D strategies are too slow and antibiotics have been less of a priority in recent years. New classes of antibiotics are urgently needed and I believe that whole community-based products will be high yield

and effective in treating infections associated with high numbers of gut-dwelling drug resistant organisms. We are pursuing a concept, which in essence is focused on combining the eco-system restoring effect of intestinal microbiome derived microbes with precision antimicrobials. In contrast to traditional antibiotics, these products will achieve their therapeutic effect through several mechanisms of action and will reinstate colonization resistance in the gut microbiome of the recipient.

### Other therapy areas?

Some would have you believe that manipulating the microbiome will become a catch-all cure for everything, but I don't think that will be the case. I do think that through the microbiome, the scientific and medical community will unlock new therapeutic avenues and novel therapeutic interventions in diseases currently associated with significant unmet clinical needs. At the present time, empirical/academic led clinical trials are being conducted across Europe for a wide variety of different diseases and infections. Should any of these be successful, then I think it is up to the industry to try and create scalable, safe and effective solutions to expand access to patients globally. At EnteroBiotix, we get excited at the prospect of collaborating with the academic community to find the next "home run" in the microbiome field and our vision is for our products to be distributed to patients all around the world.



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Formulation Development

# Natural and Synthetic

## Combining synthetic biology with microbiome science to realize new horizons in medicine.

*With Aoife Brennan, President, CEO and Chief Medical Officer at Synlogic*

### Why Synlogic?

I'm an endocrinologist by training and much of my career in biotechnology has focused on drug development for rare diseases. I've always been very interested in novel platforms and technologies for drug discovery because there is the potential to achieve so much more in medicine. Initially, I joined Synlogic as Chief Medical Officer. The synthetic biology and microbiome fields are ripe for exploitation, both in terms of the science and therapeutic potential for patients with unmet needs. Working in rare metabolic diseases is incredibly rewarding and this was a big draw for me. I was the Chief Medical Officer for around two years before being asked to step up as Chief Executive Officer of Synlogic, initially on an interim basis, but I'm now in the role permanently.

### Company focus?

There are many diseases that are still not well treated based on traditional treatment modalities and I really believe that a further understanding of the potential of bacteria, and the interaction between the bacteria that live in and around us, will unlock significant therapeutic potential. There is a growing body of evidence to support the link between what happens in the gut, on the skin and all of our body surfaces, with health and specific disease.

We don't consider ourselves to be a traditional microbiome company. We like to say that we are reimagining the potential of probiotics by transforming them into therapeutics with measurable and predictable benefits to address disease. Our approach is to marry synthetic biology (genetically modifying and creating different living cells and organisms) with an understanding of the synergistic nature and interplay between the gut lumen and different disease states to create a novel class of medicines: Synthetic Biotic medicines. We do this using our Synthetic Biotic platform; basically, we engineer probiotic bacteria to carry specialized assemblies of DNA, which allow the medicine to "sense" a patient's internal environment and respond by turning an engineered metabolic pathway on or off to elicit a therapeutic effect. Our platform can be applied to many microbes; however, the one we've chosen to focus on for our lead discovery programs is E. coli Nissle. Discovered during WW1, E. coli Nissle protected soldiers in the trenches from developing certain intestinal infections. There is a great deal of experience with this strain of bacteria, both from a safety perspective as well as understanding the genetics. We perform specific genetic engineering on the bacteria depending on the disease we want to address to give it specific therapeutic functions at the site of action. All of our drug development programs begin with an understanding of the mechanism of disease, so we have a target to guide the engineering of the bacteria.

### Therapeutic areas?

Our initial programs are focused on areas of metabolism and rare metabolic diseases, such as phenylketonuria (PKU) and urea cycle disorders (UCD). Where patients have problems metabolizing specific substrates; we can create a strain of bacteria that can consume those substrates at a very high rate. We give the bacteria orally and they function from within the gut lumen.

We are also engaged in research and development of Synthetic Biotic medicines to address more prevalent conditions, including cancer and inflammatory bowel disease (IBD). In our IBD program – a collaboration with Abbvie – we'll be discovering, characterizing and optimizing synthetic biotic-based drug candidates that modulate IBD pathophysiology. We're also working on more complex diseases, where we need to think about interactions with the immune system.

### Success stories?

Synlogic has developed very rapidly. The company was a spin out from MIT and was in the clinic within three years. I think it's very rare to have an academic spin out and reach the clinical program stage so quickly, but this rapid move to the clinic was part of our strategy to achieve proof of platform. This is also testament to the potential of genetic engineering and how quickly we can see successes with our platform.

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One of our biggest successes was generating healthy volunteer data showing dose-response relationships across two programs; essentially, these show that the bacteria are metabolically active and performing the function they were designed to perform within the human gut. And once a patient stops taking the bacteria they clear from the system with a very predictable period of time. These elements are critical for developing a GI-based living therapeutic and being able to fully understand dosing.

### Manufacturability?

In early development, strains are being grown at a very small scale, but the bacteria's behavior may change with scale up. Before we declare a clinical candidate, we will assess manufacturability. Occasionally, a strain grown in flasks looks very nice in the animal model but just doesn't behave as well when grown in the fermenter, which means we need to examine whether we can address the problem through process development – otherwise, it's back to the drawing board to engineer a new strain of bacteria. We're fortunate that our platform allows us to iterate very rapidly. Using metabolic analysis and other gene expression tools, we can identify what the issues are and then design around them to move forward again.

As well as thinking about the manufacturing process it is also important to bear in mind how patients will take the final product in the real world. If your product needs to be stored at minus 80 degrees Celsius then it's not going to work in the real world.

With both of our oral candidates, we decided to move forward into the clinic with the liquid form of the bacteria to gain experience in humans, but in parallel we have invested in the development of a formulation that is going to be more convenient for patients to take at home. Patients need something that integrates with their lives which is why we are focused on developing solid oral formulations for our gut-based programs.

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Analytical Services

# Mining the Microbiome

## Diving deep into metagenomics and culture-based analyses of patient samples to develop new live bacterial therapeutics and biomarkers.

*An interview with Mike Romanos, co-founder and CEO of Microbiotica*

### Where did your career and interest in biotech begin?

After a stint in academia as a molecular biologist, my career was focused on biotech and pharma. I started in the exciting early days in the late eighties at Wellcome Biotech, working on recombinant vaccines and biologics. Eventually, I became responsible for building and running a series of major global organizations in GlaxoSmithKline, most latterly Genomics/Platform Biology, a group of 300 people across five sites. In 2009, I started the Cambridge transgenic antibody fragment company Crescendo Biologics, which I led as CEO and CSO for six years. My passion has always been translating new molecular technologies into novel therapeutic products. In my career, I have been involved in the discovery and development of recombinant vaccines, biologics, antibodies, gene therapies and NCEs.

### How did you become involved in the microbiome space?

In 2015, I was contacted by my old colleague, Gordon Dougan FRS, then Head of Pathogen Research at the Wellcome Sanger Institute. I had first worked with Gordon in bacterial vaccines at Wellcome Biotech. I was interested in working in a new therapeutic modality but knew little of the microbiome. Gordon introduced me to Trevor Lawley, who had been building up a world-class microbiome program. Gordon and Trevor sought my help to translate their discoveries; together we designed a business plan and eventually founded Microbiotica in December 2016, with the support of Cambridge Innovation Capital, IP Group and later Seventure. It has become clear to me that the microbiome represents a paradigm shift that requires us to re-evaluate every aspect of biomedicine. These shifts and opportunities come about rarely.

### How would you describe your co-founders' heritage in the microbiome field?

Gordon is a leading authority in microbiology and vaccine design. He had recruited Trevor from the lab of the renowned Stanley Falkow at Stanford University. Trevor made key discoveries in Clostridium difficile infections and transmission, in rational design of live bacterial therapies, and in solving the challenges of mass culturing and genomic identification of human gut bacteria.

In 2012, he published a seminal paper that pioneered the design of therapies comprising defined gut bacteria to replace Faecal Microbiota Transplantation (FMT): his group showed that it was possible to replace FMT with only six particular bacteria to fully protect mice from C. difficile. This piece of work influenced the entire microbiome biotech sector in moving to defined bacterial products. By 2016, his work had gone on to address a fundamental issue in translation of the microbiome: the inability to isolate most of the gut bacteria and the resulting lack of reference genomes. In 2016, Trevor published a key paper in Nature that showed it was possible to "culture the unculturable". This one paper led to a doubling of the total number of gut bacteria that had been isolated and fully sequenced to date. The importance of this work is that it underpins a new rigor in understanding and translating the microbiome.

### Tell us a little more about Microbiotica...

Microbiotica was spun out of the Sanger Institute to exploit the groundbreaking science from Trevor Lawley's lab. We are still currently based at the Wellcome Genome Campus in Cambridge, UK, though we will move to larger facilities next year.

The company has a two-fold business strategy. First to discover and develop best-in-class live bacterial therapeutics for diseases with major unmet need, and secondly to discover bacterial drug-response biomarkers for personalized medicine with high-value drugs.

Trevor has come into the company as CSO and together we have built a powerful team of 40 staff covering all the functions required for our mission: operations, business development, microbiology, bioinformatics, translational biology and preclinical development.

### And what about Microbiotica's platform?

Microbiotica has a suite of capabilities in microbiology, genomics, translational biology and CMC that enable us to address many of the challenges in the field.

Of central importance is the world's leading Reference Genome Database and Culture Collection. Based on an unprecedented capability in mass culturing of gut bacteria, we have assembled the largest collection of full genomes (2,500 species) and are aiming to capture the majority of the world's species with full genome sequences (the "Global Microbiome Blueprint"). This gives us the capability to analyze large cohorts of patient data by shotgun sequencing to pinpoint exactly which bacterial strains are responsible for a particular phenotype (e.g., disease or therapeutic response). Such precision at scale has been lacking. In addition, we can isolate most gut bacteria from any one individual (Personalized Bacterial Bank) and bank all the bacteria for testing.

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We believe we are the first to undertake these precise studies at scale and they form the starting point for our highly differentiated therapeutic and biomarker discovery programs.

### What therapy areas is the company currently focusing on?

Microbiotica's platform is therapy area agnostic and can be used to start any program. Our first program was in C. difficile where we have developed a highly potent live bacterial therapeutic comprising defined strains to replace FMT. This program enabled us to establish and validate all our capabilities including biological testing and bacterial growth. Our most important current focus is in therapeutics for ulcerative colitis/IBD and in immuno-oncology. In ulcerative colitis, we are analyzing the bacteria responsible for the therapeutic effect of FMT from a clinical study, and in immuno-oncology we are developing therapeutics to enhance the therapeutic effect of checkpoint inhibitor drugs in cancer. Checkpoint inhibitors are revolutionary broad-spectrum cancer medicines but only a fraction of patients respond, and specific gut bacteria control the response. This approach, therefore, holds immense promise to address major medical need. We will enter new therapeutic areas in the coming year.

### Microbiotica signed a deal with Genentech last year...

Yes; we made many observers stand up and take note when we announced the strategic partnership in IBD with Genentech. It was Genentech's first deal in the microbiome area and one of the largest in the field. We secured the deal just over 18 months after our formation, worth up to $534 million, including an upfront and milestone payments and royalties.

We are using our precision microbiome platform to analyze patient samples from Genentech's IBD clinical trials of etrolizumab and RG-7880, with the aim of discovering drug–response microbiome biomarkers and therapies. These studies, involving thousands of samples and almost 50 countries, are the largest and most precise microbiome studies ever conducted. During the course of the work, we are culturing many novel bacteria and will add them to our collection towards our goal of building the "Global Microbiome Blueprint".

### Can you explain how AI fits into the company's microbiome approach?

A key challenge lies in the complexity and variability of the gut microbiome. Another challenge is the functional redundancy of unrelated microbiota, which can confound the identification of microbiome signatures linked to phenotype. While our platform can provide the most accurate characterization of bacteria in each patient with their rank order of abundance, this is not enough to discern the biomarker signature. The complexity requires that we use machine learning, testing all the different metadata so that we can identify the correct association and avoid spurious correlations. Microbiotica has built a top bioinformatics group to undertake such analysis.

### What other collaborations has Microbiotica achieved?

In 2017 we were approached by Dr Sam Costello of the University of Adelaide in Australia. He had conducted one of very few placebo-controlled trials showing FMT to induce remission in ulcerative colitis patients and wanted the benefit of the leading technology to identify the bacteria involved. We entered into a collaboration with Sam and acquired commercial rights to translate the work to a defined live bacterial therapeutic. This work is progressing very well towards a candidate. In the immuno-oncology area, we are building a clinical collaboration to analyze the microbiota in drug response in several cancers.

### What do you see as the future for Microbiotica and the industry?

The last two and a half years have been very exciting for us. We have built up a lot of momentum very quickly, which can be challenging but very rewarding. We have expanded our in-house team at a remarkable pace and will continue to grow this year. We are working in partnership with academic, clinical and industry partners who are leaders in their field and are passionate about the fast-evolving area of microbiome science. We believe this positions us at the forefront of microbiome innovation and commercialization, and to truly influence change in the sector, for the benefit of patients.

We believe that through our application of precision medicine to the microbiome, we will be able to generate effective live bacterial therapeutics, as well as novel biomarkers.

We are really just at the start of the microbiome journey. Every day brings new insights. The microbiome is emerging as having such a far-reaching influence that I believe it will influence every area of disease and emerge as the next major therapeutic modality in the industry.

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**Video**
Quay Pharma Insights Film

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