

PROBIOTICS IN TRANSITION

Authors:

Fergus Shanahan(1,2), Timothy G. Dinan(1,2),
Paul Ross(1,3), and Colin Hill(1,4)

1Alimentary Pharmabiotic Centre, University College Cork, National University of Ireland, Cork, Ireland

2Atlantia Food Clinical Trials Ltd, Cork, Ireland

3 Teagasc Food Research, Moorepark, Co Cork

4 Dept of Microbiology, University College Cork, National University of Ireland, Cork, Ireland

Abstract

Despite the hyperbole often linked with a popular research field, the scientific rationale for probiotics is sound. The probiotic concept is not new but is undergoing transition as knowledge of the gut microbiota in health and disease becomes translated to the clinic. Operationally, a probiotic represents a mimic of and/or supplement to the normal gut microbiota. Much confusion has arisen among consumers because of media misportrayals of probiotics as all being the same. However, with clarification of the molecular basis of host-microbe interactions, the selection criteria for probiotics and the delineation of their distinct mechanisms of action are improving. Most probiotics are from the genus *Lactobacillus* or *Bifidobacterium*; this is likely to change and diversify. Similarly, the development of new therapeutic strategies, such as the development of phagebiotics, psychobiotics, and genetically modified pharmabiotics, is poised to become a therapeutic reality. Probiotics represent one part of a bigger story—the gut microbiota. This unfolding story promises much, including scientific and societal impact. Few areas in biology have generated as much interest as the gut microbiota during the past few years, regularly adorning the covers of the top peer-reviewed journals. The significance of the field has not escaped the lay press and business world; one business magazine proclaimed on its cover that “*Microbes maketh man.*”(1) The attention to microbe-host interactions is due to the impact of the former on the development of the latter, the contribution of the microbiota to health maintenance, and the evidence linking changes in the microbiota with gastrointestinal and extraintestinal disorders such as asthma, obesity, and other metabolic disorders.(2–4) In addition, there is potential to manipulate the microbiota, not only by probiotics but also by basic dietary measures.(5,6) For example, a recent study of the composition of the gut microbiota in elderly people showed a strong correlation with diet and health including inflammation and frailty and underscores the importance of a diversified diet to maintain a diversified microbiota.7 Because the microbiota represents a health asset, with some microbial constituents becoming a liability in susceptible hosts, the rationale for probiotics is to enhance microbial assets and to offset liabilities. Although often defined as “live microorganisms, which, when consumed in adequate amounts, confer a health benefit on the host,”(5) a probiotic may be operationally defined as a mimic of the beneficial effects of the gut microbiota.(6,7)

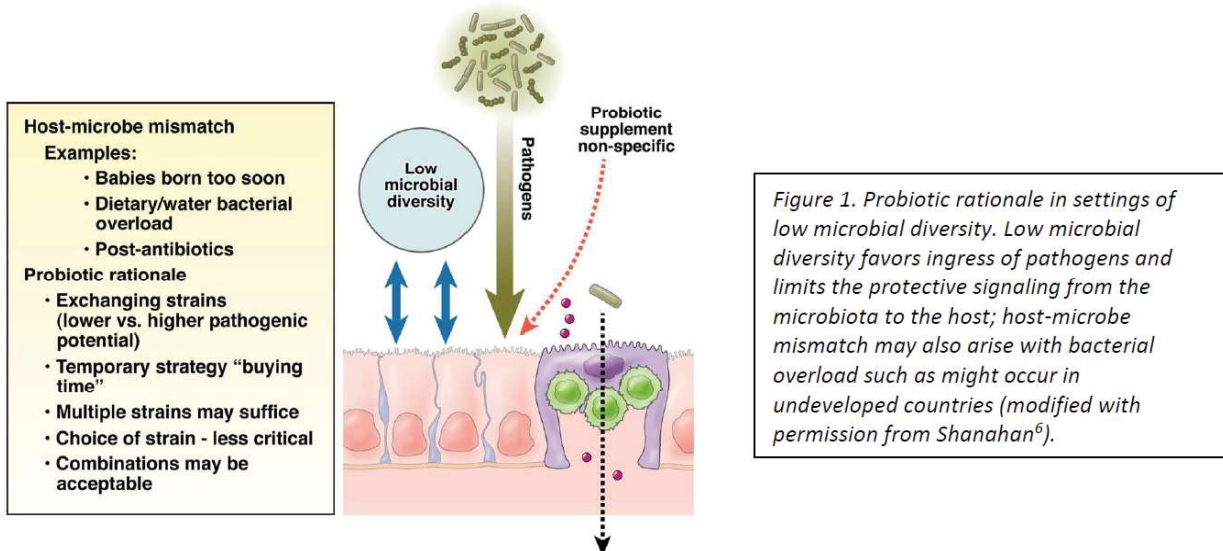
A less restrictive term, such as pharmabiotic, seems preferable to embrace all therapeutic microbial components, live or dead, including metabolites and bioactive fragments, genetically modified organisms, or even transplants of whole microbial communities.(6) This field is in transition, as the molecular basis of host microbe and of microbe-microbe interactions unfold, and has entered the realm of evidence-based medicine. Like many an expanding field, the probiotic concept has suffered from extravagant and unsubstantiated claims. However, there is solid science underlying the concept with several success stories. Analysis of the normal microbiota will yield new candidate strains, but criteria for selection of a probiotic or pharmabiotic should be based on demonstrable mechanisms of action, matched for a specific clinical indication.(8) In addition, the host-microbe interface has widened to include the brain-gut-microbiota axis, which may also be a target for therapeutic manipulation.9 Evolving concepts will be addressed in this overview; comprehensive reviews of the microbiota may be found elsewhere.(2-4)

What are the findings? Mimicking the microbiota

Consumption of a probiotic will have minimal impact on the composition or diversity of the resident microbiota, but murine studies have shown that it may have a profound influence on gene expression and metabolic activity of the microbiota.(10) Probiotic metabolites and signaling with the host may be more important. Signals from microbiota provide trophic, nutritional, metabolic, and protective input to the development and maintenance of the host digestive, immune, and neuroendocrine systems. Although the definition of a core microbiota in health is unclear,(11) it seems intuitive that broad biodiversity ensures optimal competition against pathogens and maximal microbial stimulation for

the developing host. In clinical situations where there is a low microbial diversity (such as in preterm neonates colonized before maturation of the mucosal barrier, immune system, or blood-brain barrier), a high bacterial intake (from contaminated water), or a major disturbance of the microbiota (after antibiotics), a probiotic may serve as a safe, nonspecific supplement to compete with opportunistic pathogens (Figure 1). In such circumstances, one or more of a diversity of probiotic strains might suffice. In contrast, when a specific effect (antimicrobial, anti-inflammatory, or metabolic) is required, the precise selection of probiotic strain is critical (Figure 2).

Figure 1: From Mimics to Mechanisms



As with other interventions, risk should be balanced against evidence of benefit. Third, in addition to variability in action and in efficacy across different probiotic strains, an important concern is the lack of uniform quality control in probiotic products. To offset this, consumers should opt for a reputable manufacturer. Fourth, it should not be assumed that combinations are synergistic; they may be antagonistic. Fifth, although dosimetry of probiotics is often unclear, increments of bacteria are log-fold, and more than once-daily consumption of any product should be unnecessary. In adulthood, probiotics seldom colonize the host and, therefore, must be taken indefinitely for their desired effect. Finally, for the worried well and those patients seeking only to optimize their intestinal microbiota, a probiotic should not be a substitute for a diversified nutritious diet, which is a major determinant of the composition of the gut microbiota.(7)

A Glimpse of the Future

Establishing the molecular mechanisms of action of probiotics opens the prospect of translating “bugs to drugs.” Microbial-derived antimicrobial, immunoregulatory, or anti-inflammatory molecules promise new natural therapies (pharmabiotics). Similarly, emerging evidence for a brain-gut-microbe axis⁸ has therapeutic implications for the development of psychobiotics, whereas the selective elimination of components of the microbial population with phage viruses is an old concept that may now be ready for exploitation (phagebiotics).

What Are the Roadblocks and/or Limitations?

More research, bigger and better clinical trials, and enhanced understanding of host-microbe interactions in health and disease are self-evident requirements for progress. More specific impediments at each step linking the science with the consumer must be tackled. First and most culpable are the media, with continual misinterpretation of the research and, in particular, inaccurate portrayal of probiotics as if all strains were the same. Second has been a lack of specific guidelines from regulatory agencies concerning the establishment of health claims for probiotics and, in some instances, inadequate policing of spurious claims. Third, the oversight of probiotic quality control by commercial suppliers is variable; indeed, this may be a more important safety consideration than concerns regarding the active strain. Hence, there is the recommendation to use probiotics only from a reputable supplier. Fourth,

clinicians and scientists have a responsibility to avoid hyperbole in describing their results. For example, documenting host-microbe interactions in vitro, regardless of their intrigue and scientific merit, is not the same as demonstrating a probiotic effect in vivo and cannot be used to infer a probiotic effect. A related problem is repetition of flawed or unproven concepts or imprecise language. An example of the former is the notion of using probiotics (or anything else) to “boost the immune system” in the normal population.

An example of the latter is the clichéd term dysbiosis, which gives the vague impression of an understanding of some microbial imbalance, when neither the understanding nor the imbalance exists. The word is unnecessary, often used inaccurately, and introduces bias if the intent is merely to describe a change in the microbiota. Fifth, at consumer level, there are the poor comprehension of risk/benefit analysis and inadequate critical appraisal of evidence for health claims. This is part of a bigger problem of science awareness and inadequate scientific thinking in society. Finally, managing patient expectations is a lingering caveat, particularly in relation to the notion of trying to reverse chronic disease, the risk for which might relate to the impact of the microbiota on the developing immune system in early infancy.

Because immunologic priming by the microbiota occurs in early life, the potential for altering immunoallergic disorders in adulthood by manipulating the microbiota is limited.

Conclusions

The rationale for probiotics is scientifically sound, and in some instances, mechanisms of action have been demonstrated at a molecular level. The selection of probiotic should be matched with the clinical indication. Probiotics are not alternative medicine; they are adjuncts or supplements to conventional medicine, not substitutes. The benefits are modest, as might be expected for a naturally occurring agent. While acknowledging that there is no such thing as zero risk, there is a long safety record with probiotics. However, quality control of probiotic products is nonuniform, and consumers should select a reputable supplier with a product for which there is supporting science.

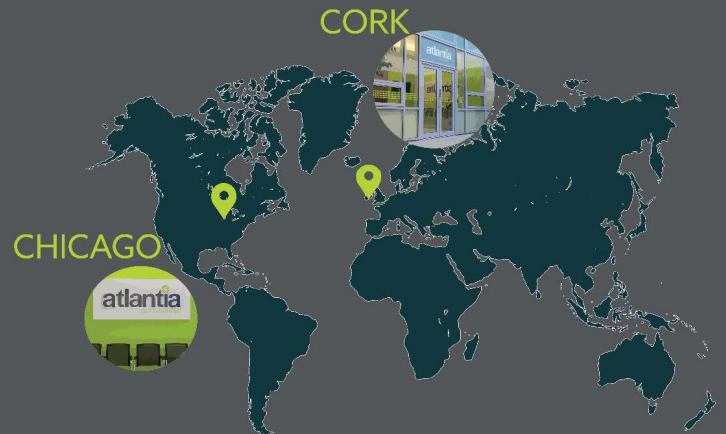
OUR CLINICAL EXPERTISE

PROBIOTICS IN TRANSITION

Atlantia Food Clinical Trials Ltd has considerable experience in conducting clinical studies exploring the potential health benefits of probiotics, in a variety of health areas including digestive health, cardiovascular health and mental and cognitive health. In this whitepaper we explore a relatively new area in the field of probiotics, namely the use of probiotics to promote mental health and wellbeing.

In light of EFSA rejections of all probiotics health claims to date, based largely on lack of strain characterisation and poorly designed human intervention studies, Atlantia has developed a "whole solution" for client companies to assist in getting a positive EFSA response for a probiotic.

- ✓ We provide end to end solutions for the entire clinical study process
- ✓ ICH GCP Standard trials
- ✓ Regulatory environment expertise, including EFSA and FDA
- ✓ One company, with multi-centre capability



Shauna Cusack

Sales Executive

Office: +353 (0) 21 430 7442
Mobile: +353 (0) 87 922 0160

scusack@atlantiafoodtrials.com



Barry Skillington

Chief Commercial Officer

Office: +353 (0) 21 430 7442
Mobile: +353 (0) 86 818 1543

bskillington@atlantiafoodtrials.com

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