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Novel opportunities for the exploitation of host–microbiome interactions in the intestine

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New sequencing technologies have dramatically increased our knowledge on the composition of the human intestinal microbiota in health and disease. In parallel, various *omics* as well as focused molecular studies have revealed novel insights in host–microbiome interactions at the cellular and molecular level. Although these studies are mainly descriptive, advanced microbiota-targeting intervention strategies are being explored, ranging from the selection of novel probiotic strains and synthetic stool substitutes, toward the better monitoring of prebiotic and dietary interventions. It can be envisaged that the efficacy of microbiota interventions will depend on the status of the microbiota of an individual at baseline, but also on genetic and physiological host parameters that determine the capacity to interact with microbes via specific receptors.

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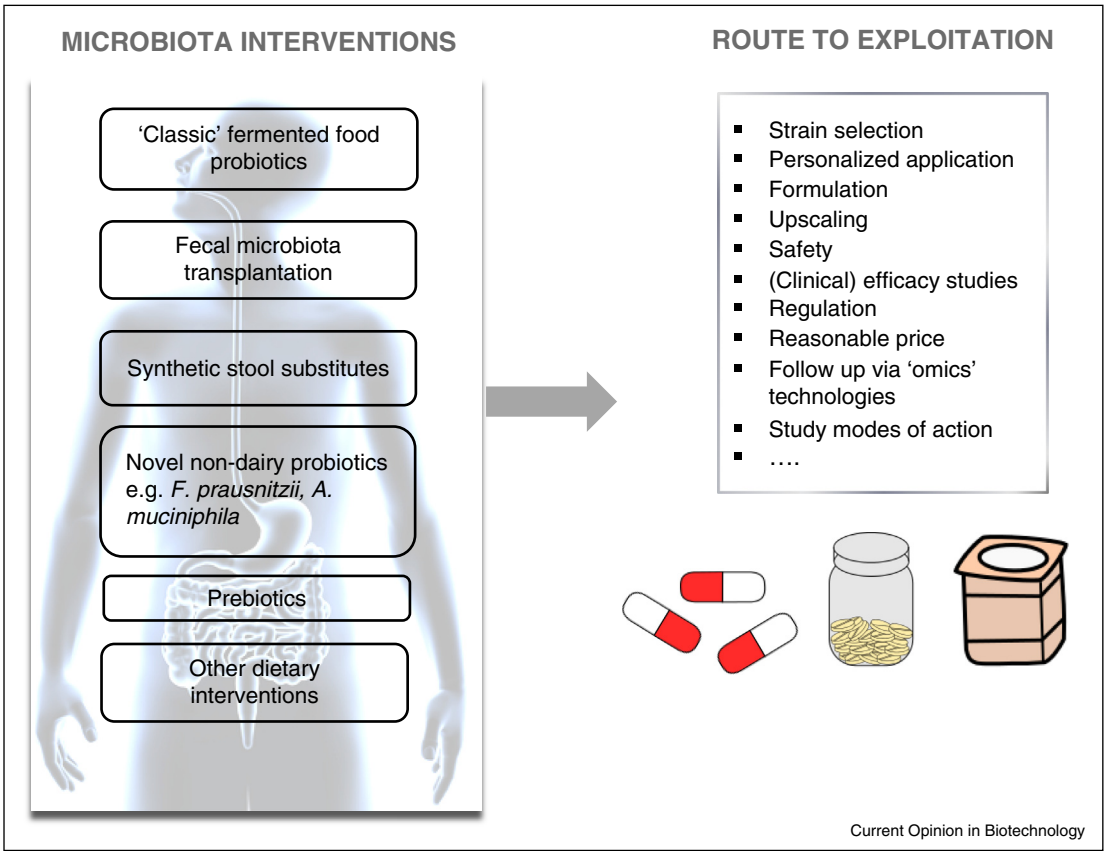
Introduction

The human microbiota has been extensively investigated in recent years using the advances in Next Generation Sequencing (NGS) and related *omics* technologies. These have provided essential information not only on the microbial composition in health and disease, but also on its impact on host metabolism and physiology [1]. It has been suggested that the human gut microbiota falls into three main compositional categories, characterized by differences in the abundance of signature taxa, referred to as enterotypes: *Bacteroides*-dominated (enterotype 1), *Prevotella*-dominated (enterotype 2) and *Ruminococcus* (enterotype 3) [2]. Whether this classification in enterotypes is applicable for subject stratification is currently debated [3]. However, follow-up studies have demonstrated that at least two of these three groups are strongly associated with long-term diets: enterotype 1 appears to be mainly associated with the consumption of animal protein and saturated fat (typical Western diet), whereas enterotype 2 is related to diets rich in carbohydrates and simple sugars, consistent with an African diet [4–7,8•]. The enrichment of specific bacterial communities in our gastrointestinal tract (GIT) appears to be directly linked to their function in degrading the type of food we are consuming. Interestingly, the recent catalog of reference genes in the human gut microbiome of Li *et al.* [9••] indicates that on average half of the ca. 600 000 genes in an individual's microbiome are common to most humans, while approximately the other half are highly specific. Moreover, even if it was traditionally thought that the GIT microbiota is stable in healthy adults, recent evidence suggests that gut microbial communities can also be rapidly altered by short term changes in diet [10•]. Although the width of the possible opportunities for the exploitation of this novel knowledge is at present difficult to fully envisage, it is yet clear that future microbiota-intervention strategies will go beyond the 'classical' probiotic, prebiotic and synbiotic applications. In addition, also host genetic and physiological factors should be taken into account to develop more personalized approaches. Here, we aim to discuss two possible exploitation directions of recent knowledge on host–microbiome interactions.

Development of novel non-dairy probiotic and microbiota targeting interventions

Traditionally, the application of probiotics, especially *Lactobacillus* and *Bifidobacterium* species, has been orientated toward fermented foods, especially dairy products [11]. The market of food supplements and probiotics in pharmaceutical tablets has also increased significantly during the last decade [12]. However, the recent success stories of fecal microbiota transplantation (FMT) appear to cause a revolution in the translation of microbiota-knowledge not only to clinical, but also to broader consumer applications (Figure 1). Although the benefits of FMT have been best documented for the treatment of *Clostridium difficile* infection [13], FMT is also explored for the prevention and treatment of other disorders associated with the GIT microbiota, such as diabetes

Figure 1



Different microbiota targeting strategies and their route toward exploitation.

mellitus and obesity. For instance, a pilot trial has shown through FMT that the gut microbiota from lean donors increased the insulin sensitivity of obese subjects [14•]. Nevertheless, to bring the benefits of FMT to the broad public, it is clear that major advances in safety (e.g. transmission of viruses and pathogens), product development and formulation of the microbiota constituents are still necessary. One solution for the safety issues could be cryopreservation of own processed stool samples, similar as for blood and germ cells. However, this cannot be done retrospectively for patients already having a dysbiosis and will definitely be at a high cost. Moreover, timing of sampling before onset of dysbiosis would be crucial. Alternatively, many different groups are now developing an optimal, minimal synthetic mixture of human stool bacteria that have the same clinical benefits as FMT. For instance, a study that has attracted a lot of attention is the 'rePOOPulate' study with a stool substitute of 33 phylogenetically diverse isolates from a healthy donor, which was able to treat two patients infected with a hypervirulent *C. difficile* strain within 2–3 days [15••]. However, this study is also often criticized because it only included two subjects. Apparently, regulatory issues are currently imposing a burden on the further development of FMT and synthetic alternatives, but scientists and regulatory authorities such as the US Food and Drug Administration (FDA) are gradually joining forces to work out solutions and applicable directives [16]. Appropriate regulation would also pave the way for carefully screened and processed material to be made available through stool banks, because it is unlikely that the same mixture will be suitable for all conditions.

In the synthetic 'rePOOPulate' mixture, several species were included that are already being studied for several years as novel generation probiotics. Among them, the obligate anaerobe *Faecalibacterium prausnitzii*, one of the most abundant bacteria in the human gut microbiota, has attracted a lot of attention. This bacterium appears to show a clear anti-inflammatory effect in *in vitro* and *in vivo* colitis studies [17]. The abundance of *F. prausnitzii* is also suggested to be a good indicator for intestinal health [18], as a lower proportion of this bacterium is associated with diseases such as Crohn's disease, colitis, acute