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The next giant step for microbes

A microbiome therapy is approved by the FDA for treatment of *Clostridioides difficile*. What's next?

Our gut microbiomes are complex, consisting of hundreds of bacterial species. These bacteria influence not only the activity of our gut, but also our neural development and response to drug treatments. It has proven difficult to determine the links between the microbiome and human health, and until recently, no microbiome-based therapies were approved by the US Food and Drug Administration (FDA) or the European Medicines Agency.

On 30 November, after a series of six clinical studies, including two phase 3 studies, the FDA approved Rebyota from Ferring Pharmaceuticals for the treatment of recurrent infections of *Clostridioides difficile* (*C. diff*) where traditional antibiotics are not effective. Rebyota is taken from stool of uninfected individuals. Healthy donors are screened for pathogens and their fecal matter is rectally transferred to a patient's gut, where the microbial community is re-established. This is a more standardized, stabilized version of a complete fecal transplant as it has been practiced up until now, where the entire microbiome of one organism is transferred to another, either in a capsule taken orally or via colonoscopy. The approval committee noted a 70.6% success rate after 6 weeks in preventing recurring infections of *C. diff* after the treatment, compared to 57.7% for placebo recipients. This improvement is modest but significant.

There are a few more candidates seeking approval for prevention of recurrent *C. diff* infection, including two oral candidates, one from Finch Therapeutics (CP101) and one from Seres Therapeutics (SER-109). CP101, like Rebyota, contains a range of bacterial species taken from a healthy human donor. SER-109 is made up only of highly purified, living Firmicutes spores intended to compete with *C. diff*.

Fecal transplants are performed to treat *C. diff* or other conditions; however, the science behind this is far from precise, and there have been few technical advances because it is difficult to know what species are present within a sample; because there can be significant variability between samples; and because there is no way to finely manipulate them. This issue of sample heterogeneity is also present in Rebyota and other therapies in clinical trials, although there are a few differences. The donor microbiomes in these trials are thoroughly screened for pathogens that could cause illness in the recipient, which does not usually happen in less regulated fecal transplants. Perhaps more importantly, Rebyota is administered after antibiotic treatment, which would lead to decreased numbers of patient microbes overall, giving the donor species more of a 'clean slate' to colonize. Even so, it is not known how variability from one sample to another could affect the outcome of a transplant.

Rebyota is a turning point for microbiome therapy and an advance over traditional fecal transplants. It sets a precedent for approvals using more standardized fecal samples worldwide, and the approval of other drugs is likely to follow, especially if it sees commercial success. The questions remain, though, of what species are contributing to clinical success and how scientists can further optimize these results. Also, what else might microbiome products do for us? Clinical trials using fecal transplants to treat inflammatory bowel disease, ulcerative colitis, cancer or obesity have brought disappointing results, likely as a result of complicated interactions between transferred microbes and the microbes already present in a patient's gut.

To begin to address the question of optimization, a study in *Cell* introduced a defined in vitro community of 119 of the most prevalent human gut bacterial species (hCom2) into mice. Perturbations at the microbe level of these species can lead to biological insights into how these species function together in a living system. This is not the first synthetic microbial community, but it is the largest to date, and the most similar to a human gut microbiome. This means that future studies or preclinical tests coming from the use of hCom2 in mouse models of diseases such as inflammatory bowel disease or ulcerative colitis could be more clinically relevant to humans.

While it would help to know which microbes are having the most clinical effect in humans, it would also help to know how they are generating this effect. Microbes interact with host cells through a variety of small molecules and signaling peptides, and instead of transplanting microbial communities, it is possible that small-molecule treatments could be influential, for known infections such as *C. diff* or for general improvement of human health.

There is no shortage of biotech startups looking at these questions. Vedanta Biosciences is developing oral drugs that are designed to deliver defined bacterial consortia to treat diseases linked to the microbiome, including *C. diff* and inflammatory bowel disease. Enterome is looking to design medicines based on personal gut commensals, looking specifically at the interactions between the microbiome and the immune system to treat inflammatory bowel diseases such as Crohn's and ulcerative colitis and to boost cancer immunotherapies. Others like Viome will analyze your microbiome and provide personalized recommendations for diet and supplements, which it can also supply.

While it is exciting to see a microbiome therapy gain FDA approval, there is much potential here for growth. Researchers will have to knock out single species, or add in others, in disease models. Companies such as Federation Bio in the United States or BiomeBank in Australia are attempting to put together curated gut microbiomes for treatment of diseases ranging from recurrent *C. diff* to ulcerative colitis and Crohn's disease. hCom2 consists of the most common gut microbial species found in humans, but it is far from a complete replica of the human gut community. We need a deeper understanding of the principles behind how these communities interact, as well as better ways to determine all of the interacting members, before we can understand how they will influence other cell types and disease states. And there are other human microbial communities such as in the lung or skin that have their own dynamics. We will still need to understand better how small inter-human variation will influence any results shown in mice. The number of microbiome-related startups shows that the money and interest are there, when the science catches up.

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