Health care

Enhanced understanding of the microbiome is helping medicine

No guts, no glory

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WHEN, at the turn of the century, the first human genomes were sequenced, many biologists felt they had had delivered into their hands the keys to unlocking numerous puzzles about disease. Since then there has indeed been a fruitful effort to understand how the thousands of human genes which control hormones, enzymes and other molecules of the body serve to regulate health. But, in an unexpected turn of events, it is also no arent that the human genome is not

times the number in the human genome alone. If the bacteria in question were doing little more than swimming around digesting lettuce, this would be of small consequence. But they are doing much more than that.

The members of the microbiome, as this community is known, are, to a surprising extent, partners of humanity. And when that partnership goes wrong, the results can be dreadful. Inflammatory bowel disease, autism, multiple sclerosis, obesity, diabetes and chronic-fatigue syndrome all seem to have links with dysbiosis, as an imbalance in the microbiome is known. Only this month, there was news that human gut microbes influence the way patients respond to a popular new type of cancer treatment called immunotherapy. Certain sorts of bacteria are abundant in patients who respond well. Antibiotics that kill these bacteria render immunotherapy less effective.

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That finding illustrates an important idea. In effect, the antibiotics are editing the collective bacterial genome by removing from it genes that somehow assist immunotherapy. Much effort is now going into developing ways of editing the human genome, in order to improve human health. This is hard to do. But editing the microbial genome, by adding or subtracting particular species—and thus the genes they carry—is in principle far easier. That, too, could lead to improvements in human health. And many hopeful firms are now pursuing this idea.

Gut instincts

bacteria, from healthy people into sick ones. It is an idea that goes back at least 1,700 years, which was when Chinese doctors began to use what was euphemistically called "yellow soup" to treat patients with severe diarrhoea. In a similar vein, warm camel dung has been employed in some parts of the world to treat dysentery.

These days, such faecal microbial transplants (FMTs) are used mainly to deal with the rampant multiplication of a diarrhoea-causing bug called *Clostridium difficile* in patients who have been heavily treated with antibiotics. The transplant alters the composition of the recipient's microbiome in ways that make it hostile to *C. difficile*. A great deal of work has been directed to refining FMTs, both for use in *C. difficile* infections and, potentially, for treating other diseases tied to dysbiosis. New, encapsulated versions of FMTs are known colloquially as "crapsules".

Transplanting whole microbiomes in this way is, though, a bit crude. Rebiotix, a firm based in Roseville, Minnesota, is developing a more refined approach: a standardised liquid suspension of healthy gut bacteria. Its most clinically advanced treatment is, as might be expected, for the prevention of recurring infections of *C. difficile*. But the firm is also searching for therapies for paediatric ulcerative colitis (a form of inflammatory bowel disease), multi-drug-resistant urinary tract infections, infections of vancomycin-resistant *Enterococci*, and hepatic encephalopathy. This last illness is one of the most common complications of end-stage liver cirrhosis. Data suggest that part of its cause is ammonia generated by gut bacteria.

Other firms are focusing their efforts even more precisely, by selecting and delivering only the microbes they believe are beneficial. This is an approach sometimes known as "bugs as drugs". Researchers at Seres Therapeutics, in Cambridge, Massachusetts, for example, think that suitable combinations of particular microbes can catalyse shifts in entire bacterial ecosystems—specifically, from ones that support disease to ones that support health. To this end, the firm is creating proprietary mixtures with particular purposes. One of its clinical trials, for the treatment of recurrent *C. difficile* infection, failed and is being re-run with an altered design. A second is for ulcerative colitis. A third is intended for first-time

The opposite approach to adding such "good" bacteria (and thus their genes) to the mix is to subtract the bad ones. That is the strategy employed by C3J Therapeutics, in Marina del Rey, near Los Angeles. This firm is developing an antimicrobial peptide (a small protein molecule) aimed specifically at *Streptococcus mutans*, a bug that lives in the mouth and which is widely believed to be the microbe mainly responsible for dental caries. C3J's drug, currently being tested for efficacy, is a non-specific antimicrobial peptide that has been joined with another peptide which binds only to *S. mutans*. Removing *S. mutans* leaves a vacant niche in the mouth. Although this is quickly filled by other species of *Streptococcus*, they are associated with a lack of cavities.

Another way to subtract components of the microbiome is to use viruses, known as bacteriophages, that attack particular bacterial species. EpiBiome, in San Francisco, and Eligo Biosciences, in Paris, are both hoping to deploy phages selectively against specific bacteria—something that would create an extremely refined form of antibiotic. EpiBiome is trying to isolate the phages which are most effective in killing harmful bacteria. Eligo is attempting to fit phages out with a form of gene-editing technology that will cut up a bacterium's DNA, thus killing the organism.

Editing bacterial genomes is also on the agenda of Blue Turtle Bio, in San Francisco, and Synlogic, in Cambridge, Massachusetts. Both companies want to engineer gut bacteria to deliver a constant supply of such things as the enzymes missing in genetic diseases like phenylketonuria (in which the absent enzyme means a chemical called phenylalanine can build up to toxic levels).

Only connect

One last microbiome-related approach to medicine is to try to identify exactly which microbe-produced substances are affecting human health, whether for good or ill. This is of particular interest to established pharmaceutical firms. They hope such knowledge might lead to the sorts of products they are adept at making. A year ago, for example, Bristol-Myers Squibb, a leading immunotherapy firm, announced a tie-up with Enterome, a Parisian company. Their joint intention is to develop drugs and diagnostic techniques based on the gut microbiome. Meanwhile, Second Genome, in San Francisco, has started [illegible] the apparent connection

intervention may be possible.

Isabelle de Cremoux, the boss of Seventure, a French venture-capital firm that has many microbiome-based investments, observes that the first bets in this area were generally connected with gastroenterology, because that is pertinent to the part of the body where the bugs actually live. But, she says, scientific publications about dysbiosis have turned increasingly to cancer. She expects biotech firms to follow. Indeed, two of those she has invested in, Enterome, and also Vedanta Biosciences, in Cambridge, Massachusetts, have started to focus on oncology.

The idea that the gut's microbial passengers can influence the progression of cancers sounds, on first hearing it, an extraordinary one. But the multiplicity of microbial genes is such that some are almost bound to have side-effects of this sort. It is certainly a long way from yellow soup to immunotherapy. The journey, though, looks as if it will be a rewarding one.

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