Probiotics are ‘enticing target’ for gene editing — but is CRISPR up for the challenge?

Every morning I pop a Pearl probiotic. I try hard not to drop it, for the tiny, slippery yellow sphere bounces, is impossible to pick up, and cats love to bat them into unreachable domains.

A probiotic is, technically speaking, a population of live microorganisms that confers health benefits on the multicellular organism that they inhabit – such as a human. Probiotics alter the bacterial, viral, and fungal milieu within and on us – our microbiomes – in ways that ease digestion, counter inflammation, strengthen the gut lining, affect brain function, and even squelch tumors.

Each Pearl – or other variation on the probiotic theme – delivers billions of *Lactobacilli* to the twists and turns, nooks and crannies, of the human host’s intestines, maintaining the microbial community within and keeping digestion flowing along smoothly. Other commonly used probiotics are *Bifidobacterium* and the yeasts *Saccharomyces cerevisiae* and *boulardii.*

Image not found or type unknown
c ncbwgqempmpv bsmj large
Credit: Nature’s Way

Borrowed from bacteria

Researchers are using the gene editing tool CRISPR to improve upon naturally-evolved human microbiomes, to build a better probiotic. CRISPR technology can introduce quality control and perhaps also tailor microbial activities in a reproducible manner, aiming to improve upon and standardize the dynamics of how the helpful microbes inhabit our insides. But will it, can it, improve upon nature?

The molecular tools of CRISPR were borrowed and developed from the natural immune response of bacteria to viruses – bacteriophages – that infect them. CRISPR reinvented as a tool can enable the precise combining of and swapping of genetic instructions between and among microorganisms in ways that might not occur in nature. The technology can also endow specific species with novel characteristics that could benefit human hosts.

Probiotics are an enticing target. Already, engineered probiotics have been used to treat metabolic disorders like inflammatory bowel disease and obesity, single-gene conditions like PKU, and bacterial infections common in people who have cystic fibrosis. Probiotics can also be tweaked to minimize development of antibiotic resistance.

A recent paper in *BioDesign Research*, CRISPR-Cas-Based Engineering of Probiotics, from investigators at several Chinese research institutions, contributed to the report.

They write:

> *Genome engineering of probiotics, including the editing of the genome to introduce, remove, or modify phenotypes, will improve their tolerance to stress during food production, promote their survival in the gastrointestinal tract, or enhance their probiotic function. The development of*

> *genome engineering and synthetic biology has greatly promoted the construction of novel probiotic strains with desired functions, which has facilitated the treatment of metabolic disorders, inflammation, pathogen infection, and even cancer.*

The role of evolution

Human microbiomes have evolved over many millennia, molded by and attuned to the viruses, bacteria and other single-celled microbes, and fungi that dwelled in the digestive tracts of our ancestors.

Several species of australopithecines, for example, lived in Africa 2 to 4 million years ago. They overlapped with the species of *Homo* that would persist and eventually give rise to the archaic humans (Neanderthals and Denisovans), more than 200,000 years ago.

These ancestors dwelled in geographically limited areas. Over deep time, their microbiomes came to reflect the diversity of species that lived on and in them. Such a natural microbiome is far different from those of people living today, able to eat diverse foods from many places.

That’s a lot of evolution, as well as symbiosis. The driving force of evolutionary change, natural selection, favors inherited traits that enable an organism to survive to reproduce, while eliminating traits that impair reproduction. Natural selection, then, would have sculpted microbiomes.

And so modern human microbiomes emerged over millennia in ways that enabled their hosts – our forebears – to have healthy, fertile offspring. Can a biotechnology, even one borrowed from bacteria to begin with, accomplish as complex an action as the natural evolution of microbiomes? I’m not so sure.

Stick to single-gene challenges?

CRISPR may make sense for replacing a single mutant gene, like the one behind sickle cell disease, for which a CRISPR-based gene therapy was recently approved. But emulating a microbiome, a complex assortment of cells and viruses, is, I think, a technically more challenging venture. Sometimes, nature may be better.

Meanwhile, though, researchers have come up with eclectic but more focused applications of CRISPR technology, which can add, remove, replace, or fix genes. The goals include:

Refining fish farming

CRISPR can remove genes that encode hormones that catfish require to reproduce. With additional genetic modifications, the fish can be raised on farms where the hormones are added to the water. They cannot survive in the wild.

Bringing back extinct species

"De-extinction" replaces genes in modern organisms with counterparts from extinct relatives, such as an elephant with mammoth genes, or a heath hen with chicken genes. *DNA Science* recently covered perfumes resurrected from extinct plants, but using older and less precise recombinant DNA technology.

Limiting spread of infectious diseases

Harness CRISPR to introduce genes into disease vectors, such as mosquitoes and ticks, which render them infertile. Or, add genes to arm a host species to resist a specific infectious disease. CRISPR can perhaps even swap in a mutation (*CCR5*) to provide resistance to HIV.

Creating organ donors

Introduce human genes into the genomes of pig fertilized ova to create an animal whose cell surfaces the human immune response will not reject when pig organs are transplanted.

Adding traits to show animals

Introduce genes for valued traits (such as fur color, body size, and stamina) into pets or show animals in just one or two generations.

Beef production

Add a gene conferring a short, slick coat that enables cattle to tolerate heat. And at the same time, remove the distinctive sialic acid molecules that dot the surfaces of beef muscle cells, causing inflammation in human burger lovers.

With CRISPR, possibilities are limited only by our imaginations. But we perhaps shouldn't bite off more than we can chew!

Ricki Lewis has a PhD in genetics and is the author of the textbook Human Genetics: Concepts and Applications, soon to be published in its fourteenth edition. Follow her at her website www.rickilewis.com or X @rickilewis

A version of this article was originally published at PLOS Blogs and has been republished here with permission. PLOS can be found on X @PLOS