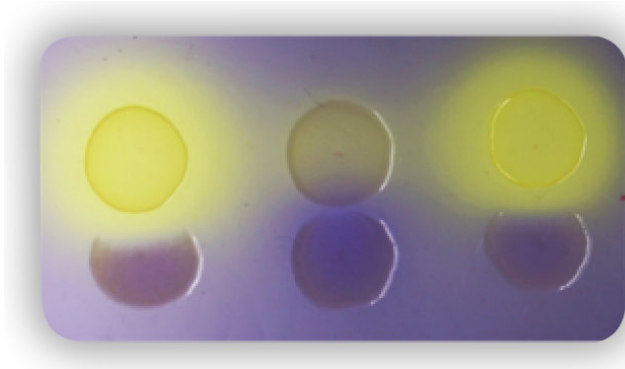


Turning the tables on the cholera pathogen

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This plate assay shows how normal *L. lactis* bacteria (top row) can suppress the growth of *V. cholera* (bottom row). Normal *L. lactis* bacteria (upper left circle) acidify the medium around them (yellow color) and hinder *V. cholerae* (lower left circle) from growing in this area. A *L. lactis* mutant strain unable to acidify the medium (middle upper circle) has lost its acidifying ability and cannot suppress the pathogen anymore, whereas a repaired mutant *L. lactis* strain (upper right circle) both abilities again. Credit: Wyss Institute at Harvard University

Recent cholera outbreaks in regions that are ravaged by war, struck by natural disasters, or simply lack basic sanitation, such as Yemen or Haiti, are making the development of new and more effective interventions a near-term necessity. Sometimes within hours, the water- and food-borne diarrheal disease caused by the bacterium *Vibrio cholerae* can lead to severe dehydration, putting victims' lives at immediate risk, especially if rehydration and antibiotic therapies are not readily available or started early enough. The World Health Organization has made it a top priority to identify cholera-managing measures and a cost-effective diagnostic test to detect *V. cholerae* early on in individuals that may help prevent its spread.

Now, researchers at Harvard's Wyss Institute for Biologically Inspired Engineering, the Massachusetts Institutes of Technology (MIT) and Boston University, led by James J. Collins are reporting a two-pronged probiotic strategy in

Science Translational Medicine that is able to suppress *V. cholerae*'s colonization of the intestinal tract in mice and to indicate their presence by simple stool sampling. The approach's first arm leverages the ability of another bacterium normally found in certain foods, *Lactococcus lactis*, to create an inhospitable intestinal environment for *V. cholerae*, while its second arm incorporates a synthetic gene circuit into *L. lactis* that senses a secreted signal from *V. cholerae*, enabling its detection in the animals.

"Our probiotic strategy presents a conceptually new way to prevent and diagnose cholera infection. First, we harnessed a naturally occurring interaction of the cholera pathogen with the microbiome as a 'living therapeutic' and then use that interaction to engineer an organism carrying a synthetic sensing circuit as a 'living diagnostic'," said Wyss Institute Core Faculty member James Collins, Ph.D., who also is the Termeer Professor of Medical Engineering & Science at Massachusetts Institute of Technology (MIT) and a Professor of Biological Engineering at MIT. "Further translated into human conditions of *V. cholerae* infection, it could offer an inexpensive and extendable point-of-need intervention for managing cholera in populations at risk of outbreaks."

Collins also is faculty leader of the Wyss Institute's Living Cellular Devices initiative, which genetically re-engineers living cells as programmable devices for various biomedical applications.

Prompted by the early observation that *V. cholerae* bacteria are sensitive to acidic conditions, the team investigated whether *L. lactis*, a safe bacterium that ferments the milk sugar lactose into [lactic acid](#) and used in the production of buttermilk, could be used as a probiotic intervention against *V. cholerae*. They demonstrated first in co-culture assays in vitro that normal *L. lactis* bacteria efficiently inhibited the growth of *V. cholerae*, while a mutant strain of *L. lactis* that could not produce lactic acid anymore had lost this inhibitory potential. When the researchers co-introduced *L. lactis* and *V. cholerae*

into infant mice—which can be orally infected with the cholera pathogen much more easily than adult mice—they found that *L. lactis* significantly increased the likelihood of animals to survive the *V. cholerae* threat, and decreased *V. cholerae*'s ability to thrive in mouse intestinal tissue. Again, the effect depended on *L. lactis*' ability to produce lactic acid, and thus to generate an inhospitable microenvironment for *V. cholerae* in vivo.

"The lethal dose of *V. cholerae* is very high. By suppressing the pathogen's development in the early phases, our approach slows the progression of the disease and wins the body valuable time to develop its own immune response to clear out the pathogen," said co-first author Ning Mao, Ph.D., who worked on the project as a graduate student in Collins' group. She now is a consultant at Simon-Kucher & Partners in their Life Science Division in Singapore. The two other co-first authors on the study are Ewen Cameron, Ph.D., a former postdoctoral fellow and expert on cholera microbiology on Collins' team who now is Senior Associate at Flagship Pioneering; and Andres Cubillos-Ruiz, Ph.D., another postdoctoral fellow working with Collins.

The team then extended their approach by using *L. lactis* bacteria to develop a living diagnostic. "Essentially, we used synthetic biology to make *L. lactis* "hear" the language that *V. cholerae* bacteria use to talk to themselves," said Mao. Essentially, the researchers grafted a so-called 'quorum sensing' receptor from *V. cholerae* for a signal called CAI-1 to *L. lactis*. The sensation of CAI-1 normally allows the pathogen to continuously gauge the density of its population within the intestinal microbiome. However, in the engineered *L. lactis* bacteria, a synthetic gene circuit links the detection of CAI-1 to parts of one of *L. lactis*' own signal sensing mechanisms and additional elements to enable a reporter protein to be produced only when CAI-1 is present.

In infant mice that were dosed with both, the engineered cholera-sensing *L. lactis* bacteria and the cholera pathogen, the team could conveniently diagnose cholera infection by tracing the activity of the reporter protein in fecal pellets of the mice. Because the engineered bacteria had a lowered

capacity to create an acidic environment and actively prevent infection themselves, the team created a combined therapeutic and diagnostic probiotic intervention by treating mice with a mixture of natural and engineered *L. lactis* and demonstrated that it could simultaneously suppress and detect cholera infections.

"This study highlights how targeting the human gut microbiome with appropriate probiotics and engineered living cellular devices could lead to new therapeutics and diagnostics for management of infectious and epidemic diseases in many parts of the world," said Wyss Institute Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at HMS and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS.

More information: N. Mao et al., "Probiotic strains detect and suppress cholera in mice," *Science Translational Medicine* (2018).

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