introduced under former president Barack Obama, will not take effect until 2019.

Before 2012, published estimates of the US methane leakage rate ranged from 1% to about 8%, Alvarez says, and the lack of consensus pushed scientists to improve measurements of those rates in subsequent years. Alvarez and his team pooled data from some of these studies — many of which quantified emissions at individual facilities — and validated the measurements using aircraft surveys. The team covered regions accounting for about 30% of US gas production.

The researchers then extrapolated the figures to estimate methane leaks at the national level. The team found a leakage rate of 2.3% in 2015, compared with the 1.4% estimate from the EPA. The gas is escaping through holes in the production system, and it adds up to a lot of emissions, says Alvarez.

The findings reduce the uncertainty around the magnitude of US methane emissions, says Daniel Zimmerle, an energy researcher at Colorado State University in Fort Collins. "But I would be surprised if this would be the final word on the topic."

Because of methane's warming potential, a leak rate of 2.3% is concerning, says Robert Howarth, an Earth-systems scientist at Cornell University in Ithaca, New York. But he cautions that the study might have underestimated the actual leak rate of methane. Howarth notes that the measurements scientists used include some obtained with an instrument that — according to the device's inventor — produces systematically low numbers[2].

What's more, Howarth says, the researchers didn't look at the emissions from systems that distribute gas to urban areas, which studies suggest are considerable[3].

But Alvarez looks on the bright side. Because a substantial proportion of these leaks is probably due to faulty equipment, he sees a "tremendous opportunity" to reduce methane emissions by developing systems to quickly detect malfunctions at oil and gas facilities, and by identifying overlooked ways in which the greenhouse gas escapes into the atmosphere. ■

1. Alvarez, R. *et al. Science* https://doi.org/10.1126/science.aar7204 (2018).
2. Howard, T. *Environ. Sci. Technol.* **49**, 3981–3982 (2015).
3. McKain, K. *et al. Proc. Natl Acad. Sci. USA* **112**, 1941–1946 (2015).

MICROBIOLOGY

Bacteria deliver gene therapies

Engineered strains of Escherichia coli *and other microbes are being tested in people as treatments for a slew of illnesses.*

BY SARA REARDON

People often take medicines to rid themselves of problem bacteria. Now, a counter-intuitive approach — turning genetically modified bacteria into medicines — is gaining ground.

Several companies are testing whether engineered bacteria can treat conditions that affect the brain, liver and other organs — and even kill other, harmful microbes. But although US regulators have approved trials of several types of engineered bacterium as a form of gene therapy, questions remain about whether microbes' ability to share DNA with one another will create long-term safety risks.

The idea of using bacteria to deliver gene therapies first surfaced in the 1990s, but early clinical trials met with mixed results. Interest in the approach has increased in recent years amid mounting evidence that the bacteria that live in the body — the microbiome — can influence human health. Researchers are looking to treat disease by modifying microbes that are normally found in people or the foods they consume.

"The microbes are extremely smart and they know how to survive."

Matthew Chang, a synthetic biologist at the National University of Singapore, says that genetically modified bacteria have the potential to treat many diseases. His group is engineering the gut bacteria *Escherichia coli* and *Lactobacillus* to recognize and destroy harmful microbes[1]. "It's a rapidly growing area," says Chang, who adds that he is in talks with regulators in Singapore about starting clinical trials.

One strain of research is aimed at treating the genetic disorder phenylketonuria. People with the condition are deficient in an enzyme that breaks down the amino acid phenylalanine, which causes neurological damage if it builds up in the body. At the American Society for Microbiology's annual meeting in Atlanta, Georgia, earlier this month, researchers from the biotechnology firm Synlogic in Cambridge, Massachusetts, reported that *E. coli* modified to produce an enzyme that degrades phenylalanine, and a protein that moves it from blood to cells, reduced levels of the amino acid in monkeys' blood by more than half compared with animals in a control group. The company started clinical trials in healthy human volunteers in April, and will begin testing the bacteria in people with phenylketonuria as soon as it concludes that the therapy is safe.

Another firm, Intrexon of Germantown, Maryland, has altered *Lactococcus lactis*, a bacterium used in cheese production, to make a protein that protects skin's outer layers. One clinical trial that has enrolled about 200 people with cancer is testing whether an *L. lactis* mouthwash can prevent oral sores that are a side effect of chemotherapy. In July, the company will begin dosing people who have diabetes with a different form of *L. lactis* that produces both the precursor to human insulin and an immune protein that enhances cells' ability to respond to insulin.

Both Intrexon and Synlogic have engineered their bacteria to reduce their likelihood of establishing colonies in the body — which means that patients would have to take the microbes regularly. But other companies are pursuing treatments that would create colonies of transgenic bacteria in the body.

The biotechnology firm Osel in Mountain View, California, plans to seek US ▶

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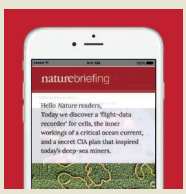

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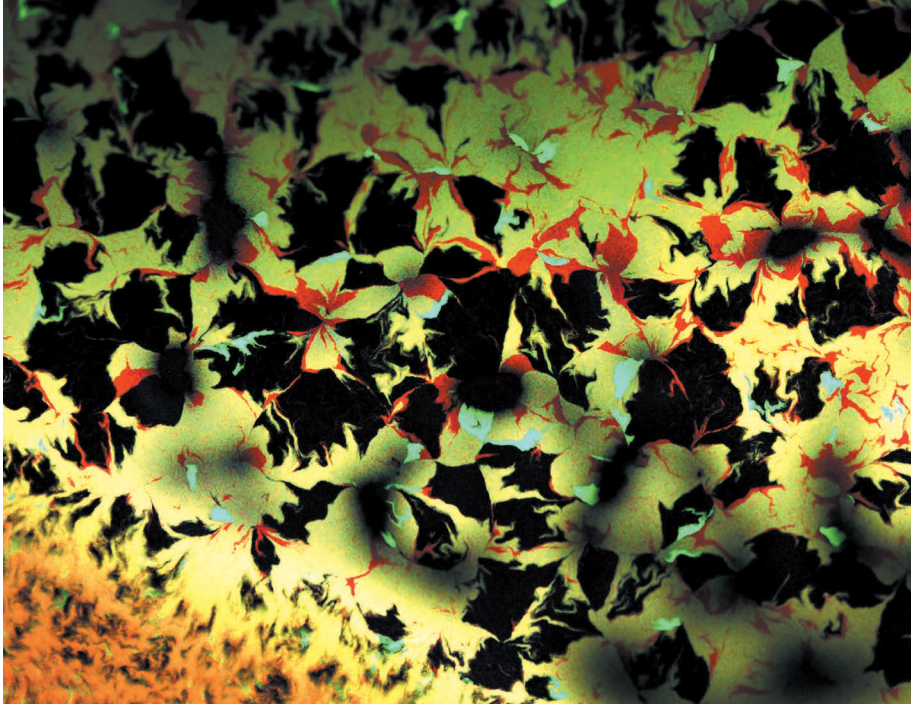

The *Escherichia coli* bacteria is being developed as a vehicle for gene therapy in people.

FERNAN FEDERICI AND JIM HASELOFF/WELLCOME COLL./CC BY

government approval this year for a *Lactobacillus* that has been engineered to prevent HIV transmission. Studies have shown that naturally high levels of *Lactobacillus* in the vagina can help to protect women against HIV[2]. Osel is attempting to enhance the bacterium's protective properties by modifying it to make a human protein that prevents HIV infection.

Challenges remain before these engineered bacteria can enter the market. There is a risk that the microbes could pass the human genes they carry to other bacteria in the body, with unknown consequences. Several companies have attempted to prevent this exchange by altering the chromosomes of a bacterium, rather than its plasmids — tiny pieces of DNA that bacteria pass back and forth. They have also built in biological 'kill switches' to prevent the microbes from surviving outside the body.

This strategy can fail, however. A group led by immunologist Simon Carding of the University of East Anglia in Norwich, UK, engineered[3] *Bacteroides ovatus* to treat colitis, an inflammation of the intestine. The group also edited the bacterium's chromosome to make it dependent on a molecule produced by naturally occurring gut bacteria.

But just 72 hours after the scientists fed the bacteria to mice, they found that *B. ovatus* had passed its modified gene to other microbes in the animals' guts — and acquired genes that allowed it to live without the molecule.

The experience caused Carding to abandon efforts to develop bacteria as therapies. "It's potentially harmful if it's not properly controlled," he says.

Synlogic, Osel and other companies say they have never observed this type of gene transfer, but agree that it is possible. "The microbes are extremely smart and they know how to survive," says Chang. It remains to be seen, he adds, whether engineering bacteria to colonize the body or die out quickly is a better approach — but the answer could emerge as the current set of clinical trials wraps up in the next few years. ■

1. Hwang, I. Y. *et al. Nature Commun.* **8**, 15028 (2017).
2. Gosmann, C. *et al. Immunity* **46**, 29–37 (2017).
3. Wegmann, U., Carvalho, A. L., Stocks, M. & Carding, S. R. *Sci. Rep.* **7**, 2294 (2017).