DRUG DEVELOPMENT

Microbiome therapy gains market traction

Wave of investment suggests drugs from body-dwelling bacteria are heading for the clinic.

BY SARA REARDON

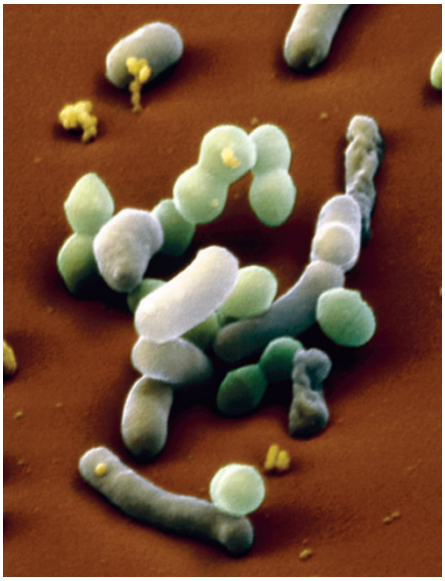
The human body teems with trillions of microorganisms — a microbial landscape that has attracted roughly US$500 million in research spending since 2008. Yet with a few exceptions, such as the use of faecal transplants for treating life-threatening gut infections or inflammatory bowel disease, research on the human microbiome has produced few therapies.

That is poised to change as large pharmaceutical companies eye the medical potential of manipulating interactions between humans and the bacteria that live in or on the body.

On 2 May, drug giant Pfizer announced plans to partner with Second Genome, a biotechnology firm in South San Francisco, California, to study the microbiomes of around 900 people, including those with metabolic disorders and a control group. "We are looking at using this as one piece of a puzzle to understand an individual," says Barbara Sosnowski, vice-president of external research and development at Pfizer in New York. A day earlier, Paris-based Enterome revealed that it had raised €10 million (US$13.8 million) in venture capital to develop tests that use the composition of gut bacteria to diagnose inflammatory and liver diseases.

Experts predict that the next few months will see a boom in such partnerships and investments, and that new microbiome-derived drugs and therapies will come to market within a few years.

Probiotics, or beneficial gut bacteria, have become a popular therapy in recent years. Television advertisements feature celebrities touting *Bifidobacterium*-laced yogurt, and consumers flock to buy pills that contain *Lactobacillus* to quell their gut disturbances and other ailments. But many physicians and scientists doubt the effectiveness of such remedies. "Probiotics may be relatively safe, but not particularly potent in terms of modifying diseases or symptoms," says Joseph Murray, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota.



EYE OF SCIENCE/SPL

Researchers are studying how gut bacteria such as *Lactobacillus* (grey) interact with the body.

But as scientists come to understand the mechanisms by which specific bacteria affect the body, many think that they can pinpoint the right combination of microbes to treat different conditions. Others aim to develop molecules that mimic a beneficial bacterium–host interaction, or block a harmful one. "Undoubtedly, the microbiome is a little drug factory in our intestine," says Justin Sonnenburg, a microbiologist at Stanford University in Palo Alto, California.

Murray's group, for example, has reported that feeding the gut bacterium *Prevotella histicola* to transgenic mice engineered to have human-like immune systems can suppress the inflammation caused by multiple sclerosis and rheumatoid arthritis. His team is hoping to develop this into a therapy with biotech firm Miomics in New York. Similarly, Vedanta Biosciences in Boston, Massachusetts, is conducting preclinical trials of a pill containing microbes that suppress gut inflammation (Y. Furusawa *et al. Nature* **504,** 446–450; 2013).

And last June, Second Genome announced a deal with Janssen Pharmaceuticals of Beerse, Belgium, to study the microbial populations of people with ulcerative colitis, in the hope of identifying new drugs and drug targets. Although Second Genome remains vague about the details of its products, president Peter DiLaura says that the company hopes to find small molecules and biological compounds such as proteins that can tweak the microbiome to ease diabetes and autoimmune disorders.

Meanwhile, one of Second Genome's scientific consultants, bioengineer Michael Fischbach of the University of California, San Francisco, is developing tools to identify molecules found on bacteria or produced by them, and which bind to receptors on human cells and affect the immune or nervous systems. "It's not just a drug-like molecule — it's a real drug being produced," he says.

Changing the balance of 'good' and 'bad' bacteria in the gut microbiome can also influence health — inflammation, for example, or even depression and anxiety. Researchers may already have a wealth of ready-made medications that can alter this equilibrium. Drugs and small molecules that have been discarded because they are not absorbed by the intestine may help to target the gut microbiome specifically, treating it as an organ.

MORE ONLINE

FRANK WALDECKER/LOOK DIE BILDAGENTUR DER FOTOGRAFEN/ALAMY

TOP NEWS

Ancient mountain range in Tibet pre-dated Himalayas go.nature.com/gkohw9

MORE NEWS

- More studies on male genitalia than on female parts go.nature.com/brfcmv
- Deepwater Horizon's legacy of methane go.nature.com/jugbn1
- Biomimetic veins deliver self-healing fluids go.nature.com/vscac8

NATURE PODCAST

Virgin males are rougher with pups; animal studies have gender bias; and droughts move mountains nature.com/nature/podcast

Sonnenburg's team, for instance, has found that a compound called sialic acid builds up in the intestine and helps harmful bacteria to take over the gut when antibiotics have killed off helpful bacteria. The researchers are now investigating whether treating mice with compounds similar to sialic acid can inhibit this harmful transformation (K. M. Ng *et al. Nature* **502,** 96–99; 2013).

And Microbiome Therapeutics, a biotechnology company in Broomfield, Colorado, is currently conducting clinical trials with two small molecules that select for 'good' gut bacteria to help people with diabetes to take up insulin more easily. Chief executive Steven Orndorff says that the company plans to present the first results from the trials next month at an Endocrine Society conference in Chicago, Illinois.

Other companies are turning the microbiome into a diagnostic tool. Enterome has created a genetic-sequencing platform that detects changes in stool microbes that warn of the onset of disorders such as inflammatory bowel disease. The firm has tracked progression of the disease in 100 such patients in a bid to avoid invasive colonoscopies.

Getting microbiome-inspired therapies to market presents a number of challenges, however. Small molecules such as those developed by Microbiome Therapeutics may be able to go through the normal drug regulatory pathway. But there may be a different or new set of regulatory hurdles for genetically modified bacteria — for example, those in development by Ghent-based ActoGeniX in Belgium and ViThera Pharmaceuticals in Cambridge, Massachusetts — that deliver anti-inflammatory agents to the gut. Other issues, including intellectual-property rights for naturally occurring bacteria, may complicate the path of products to market.

Although small start-up firms can be flexible in navigating these issues, funding and guidance from pharmaceutical giants can only help, says Bernat Olle, chief operating officer of Vedanta. In 2013, for example, Vedanta struck a deal with Johnson & Johnson, based in New Brunswick, New Jersey, to develop potential therapies for inflammatory bowel disease and other autoimmune disorders.

"The microbiome is a little drug factory in our intestine."

Pierre Belichard, Enterome's chief executive, says that such investment has been a long time coming — but companies are now flocking to microbiome research. "Doctors have been asking questions about why this new and fascinating world of science is not seen as a place to put money in," he says. "Until the beginning of this year, that was a very good question." Now, he says, investors "all want a microbiome company in their portfolio". ■

BEN MOAT

A sensor-equipped mooring that measures the strength of the Atlantic Ocean's overturning currents.

OCEANOGRAPHY

Atlantic current strength declines

But more data are needed to indicate whether the slowing is a result of human-induced climate change.

BY QUIRIN SCHIERMEIER

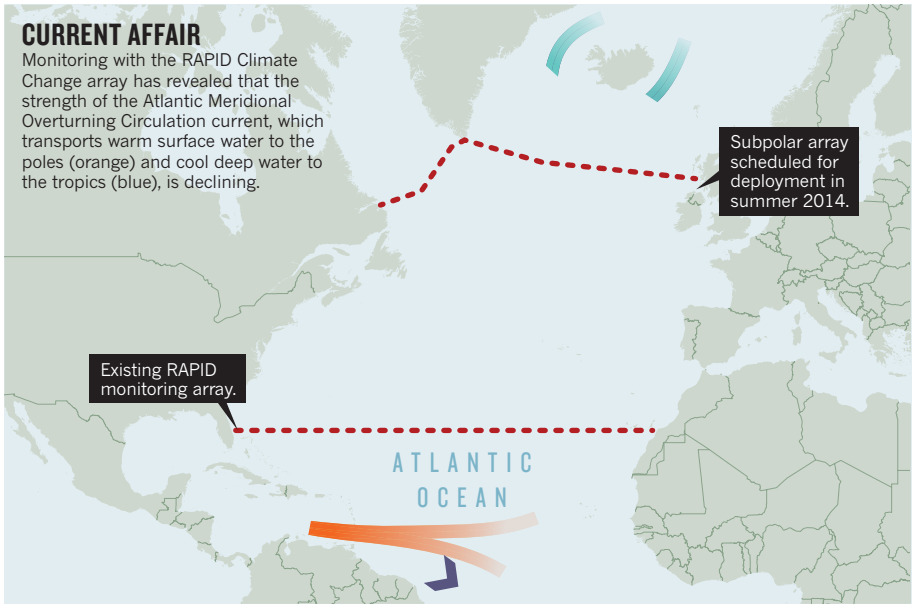
The marked slowdown in the past decade of the warm Atlantic Ocean currents that bring mild weather to northwestern Europe may be caused by natural variation and not anthropogenic climate change, as has been previously suggested.

The Atlantic Meridional Overturning Circulation (AMOC) is part of the great ocean 'conveyor belt' that ceaselessly circulates sea water, heat and nutrients around the globe. In particular, it transports large amounts of warm water from the tropics to the poles, warming the British Isles and maritime northern Europe along the way (see 'Current affair'). But since 2004, ocean sensors have detected a significant decline in the strength of the currents[1] and a cooling of the subtropical Atlantic as a result[2]. From mid-2009 to mid-2010, for example, the circulation slowed to two-thirds of its usual strength — and some oceanographers suggested that the drop caused the harsh weather in the United Kingdom and western Europe that winter (see *Nature* **497,** 167–168; 2013).

Climate scientists had speculated that the slowdown is linked to man-made climate change. But an analysis presented last month by a team of British scientists at the annual assembly of the European Geosciences Union in Vienna suggests that the AMOC's slowing could just be part of natural oceanic fluctuations. The researchers added, however, that it will take more long-term monitoring to definitively rule out climate change as a factor.

Scientists think that the AMOC might be subject to abrupt changes that have probably played a part in ancient climate events, such as the sudden temperature swings 18,000 to 80,000 years ago during the last glacial period. The AMOC's main engine — the sinking of cold, dense water to the bottom of the North Atlantic — has been identified as a potential 'tipping element' in Earth's climate system, in which small climate perturbations could push the system past a critical threshold, with potentially large consequences for humans and ecosystems[3].

Since 2004, 22 moored sensors have been deployed between the Canary Islands and



Florida along the latitude line at 26.5° north — where the AMOC emits its maximum heat. The sensor array, known as the RAPID Climate Change monitoring array, has continuously monitored the strength and temperature of the current at different depths.

RAPID measurements previously revealed[1] that the circulation weakened by 3% per year on average between 2004 and 2008, with a mean strength of 17.5 million cubic metres per second. Most of the past decade's observed decline occurred between April 2008 and March 2012, when the AMOC was around 15% weaker on average than in the previous four years. The measurements also showed that the strength of the currents varied by up to 70% from year to year, depending on wind and seawater temperature.

To find out whether the observed long-term decline lies within the range of natural yearly fluctuations, Chris Roberts, a climate scientist at the UK Met Office's Hadley Centre in Exeter who led the latest analysis, compared the observed trend with estimates of circulation strength derived from 14 state-of-the-art climate–ocean models. If the variability in modelled circulation strength were to differ substantially from observed trends, it could suggest that the decline is down to an external forcing factor such as climate change.

"It could have significant consequences for society."

Although the results suggested that the downward trend is extremely unusual, Roberts knew that models can substantially underestimate the actual year-to-year variability in the strength of the AMOC. When he and his team adjusted the models to incorporate more-realistic natural fluctuations, the downward trend was statistically in line with the expected variations. Even if the slowing continues at the current rate, the trend will not differ significantly from plausible estimates of natural variability for 18 more years, the team concluded. But it will take at least 10 more years of continuous observation to detect any influence of man-made climate-change effects, says Roberts.

"There's nothing at the moment that would suggest that something dramatically worrying is going on," says David Smeed, an oceanographer at the UK National Oceanography Centre in Southampton and a lead researcher in the RAPID programme. He suggests that the weakening of the AMOC could be because of the Atlantic Multidecadal Oscillation — a natural cycle of ocean variability in which Atlantic temperatures dip every 60 to 70 years.

RAPID, which was funded by the Natural Environment Research Council in Swindon, UK, was last year extended to run until 2020. Another array, funded mainly by UK and US science agencies, will be deployed this summer in the North Atlantic between Labrador, Greenland and Scotland to monitor the AMOC in subpolar regions. Together, data from the two arrays should help to explain the mechanisms behind the changes in circulation, says Susan Lozier, an oceanographer at Duke University in Durham, North Carolina, especially because the subpolar array is along a similar latitude to the main driver for the Atlantic Ocean circulation system.

Regardless of the cause of the AMOC's decline, if the trend persists "it could have significant consequences for society" in terms of the climate in northwestern Europe, says Roberts. Nevertheless, being able to predict the strength of the current could help to improve short-term regional climate forecasts, he says. ■

1. Smeed, D. *et al. Ocean Sci.* **10,** 29–38 (2014).
2. Cunningham, S. A. *et al. Geophys. Res. Lett.* **40,** 6202–6207 (2013).
3. Lenton, T. M. *et al. Proc. Natl Acad. Sci. USA* **105,** 1786–1793 (2008).