Collaborating to unlock secrets of the microbiome

Discovery
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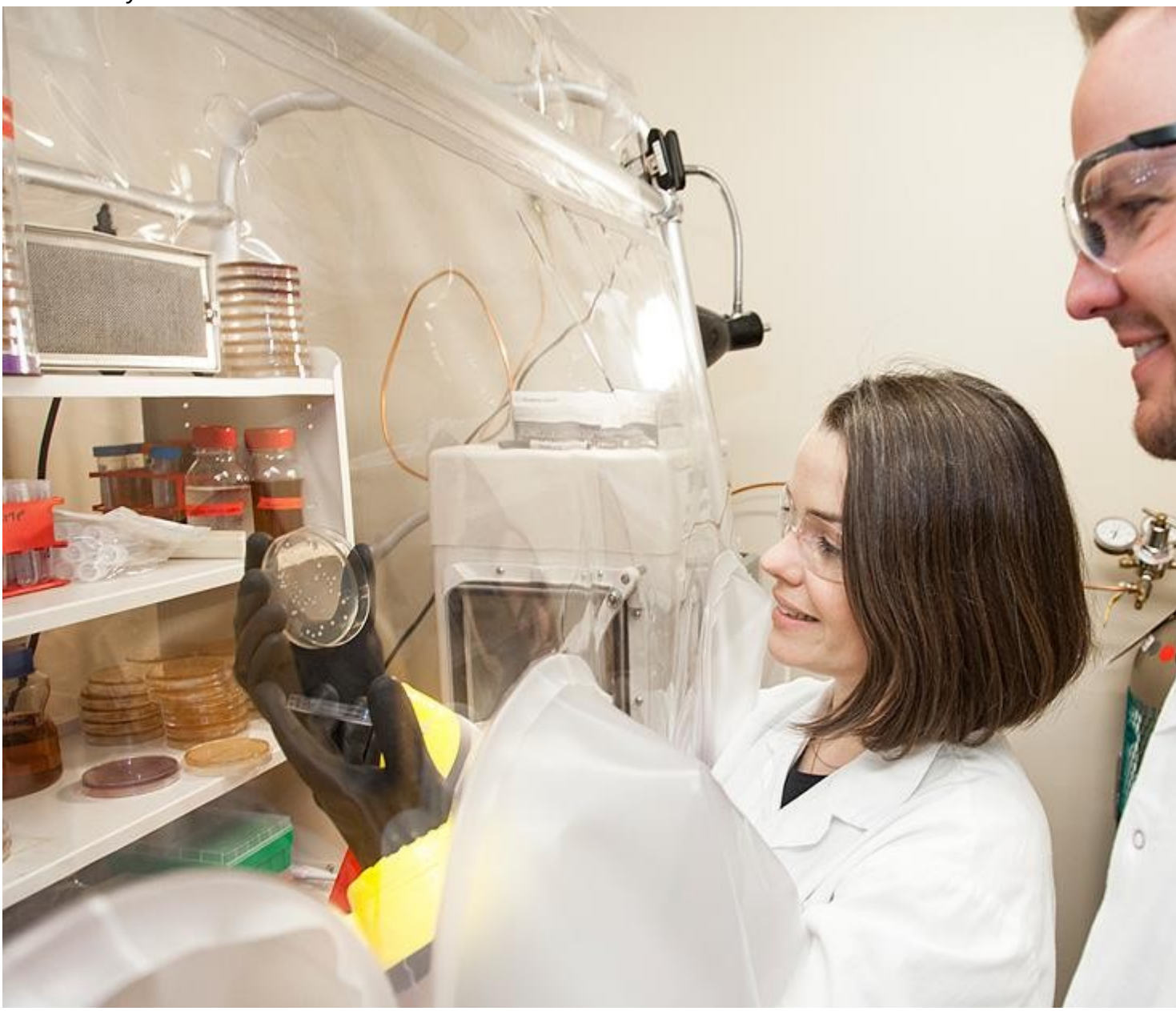
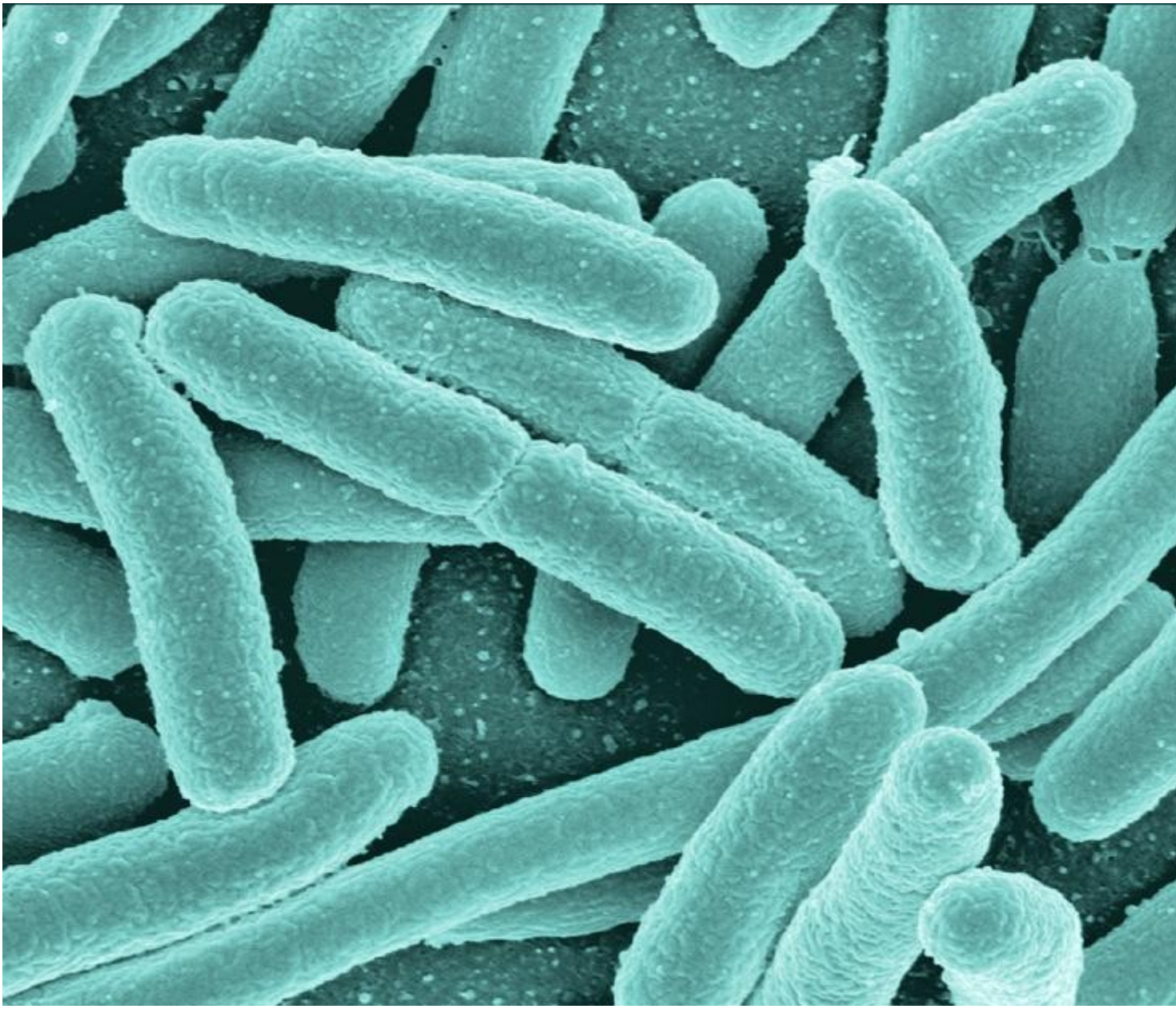


Immunologist Eva d'Hennezel and microbiologist Thomas Cullen helped unravel a mechanism by which gut microbes influence the development of type 1 diabetes in children. Here they examine bacteria grown in an anaerobic chamber with transparent plastic walls. Photo by PJ

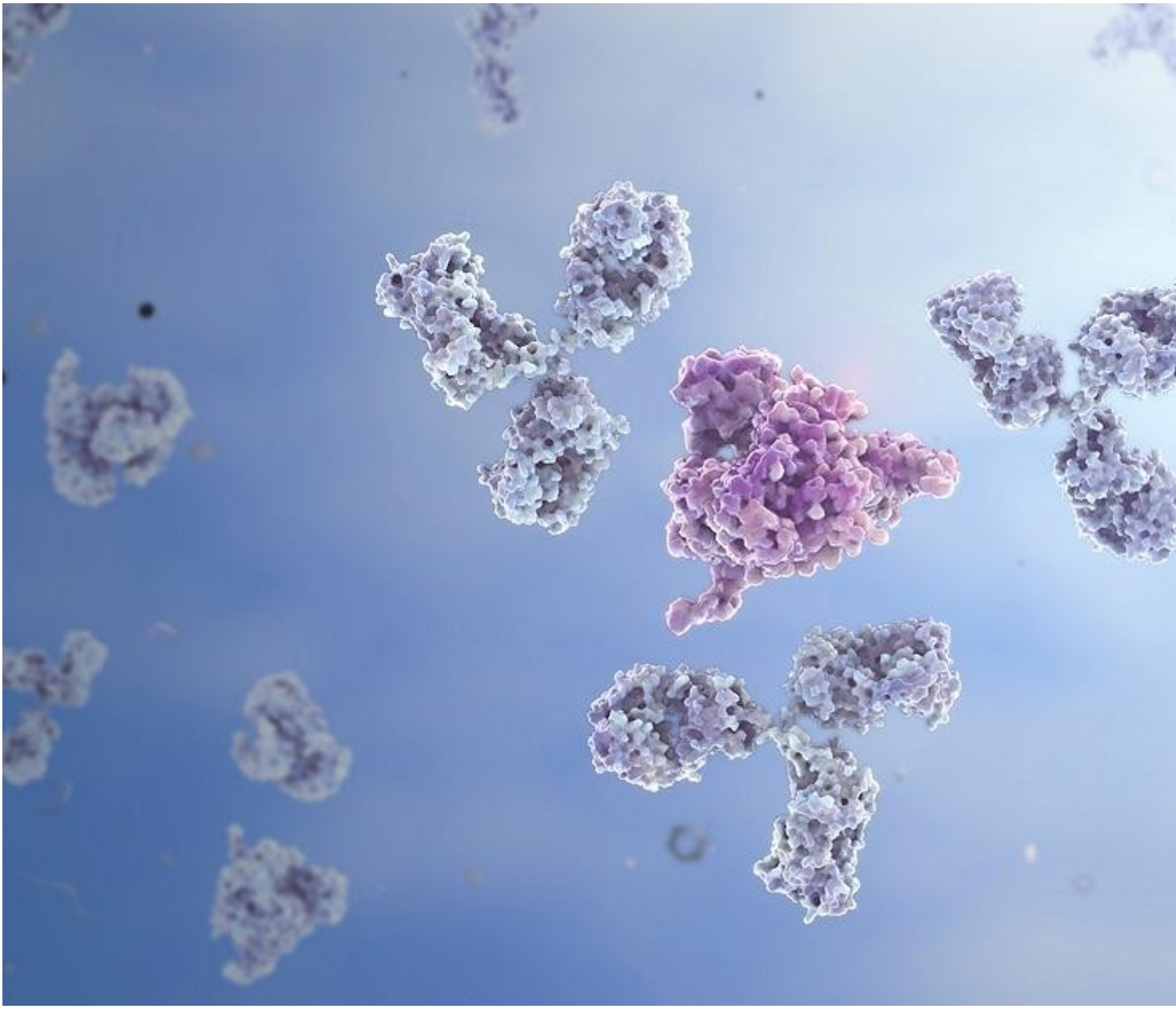
Kaszas

It’s known that children in Finland develop autoimmune diseases—including type 1 diabetes—at a much higher rate than children in Russian Karelia, despite being just next door. Standards of living are very different in the two regions. Photo by dml5050/iStockphoto



Bacteria such as these E. coli produce a molecule called LPS, which is an endotoxin that triggers an immune response. Different bacterial species contribute to the dominant forms of LPS in Finland and Russian Karelia. SEM image by NIAID

A form of LPS produced in both groups of infants is very strong, eliciting a robust immune response. A second form of LPS, one produced mostly in the Finnish infants, is much weaker and blocks the robust immune signaling of potent forms of LPS. Photo by PJ Kaszas



The weak form of LPS might be interfering with an important process in the Finnish infants: calibration of the immune system. Image of antibodies attacking an antigen by marusblanke/iStockphoto

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The microbiome has gone mainstream. Media outlets run story after story on our beneficial bugs, fueling interest in the role that bacteria living in and on the human body may play in combatting disease. Companies market probiotic yogurt and supplements, claiming that they promote health. Consumers avoid antimicrobial soaps, fearing that they'll kill "good" microbes and promote the growth of "bad" ones.

Is the hype warranted? Can we harness knowledge about the microbiome to prevent and treat disease? A team of researchers at Novartis and the Broad Institute of MIT and Harvard plan to explore the possibilities together. Their first joint discovery—on the connection between gut bacteria and the development of type 1 diabetes—appears online [1] in the journal *Cell* on April

28.

The microbiome research field is still relatively young. The first paper [2] detailing the stunning diversity of bacteria in humans was published in 1999. Since then, groups around the world have used metagenomics to characterize the communities of microbes living on our skin, in our guts, etc. In 2012, an international consortium found [3] that more than 10,000 species of microorganisms call humans home. Researchers have shown that many of these bugs play an essential role in maintaining our health, and a growing number of scientific publications link changes in the microbiome to disease.

But how the cellular and molecular mechanisms of this microbial world operate remains shrouded in mystery.

“There are a number of diseases that have been associated with changes in the microbiome, but in most cases, we don’t understand what’s happening at a gene and pathway level,” says Ramnik Xavier [4], a gastroenterologist and Broad Institute member who helped shape the collaboration with Novartis. “Are the microbes themselves triggering disease? Is it products that they make? What role does the host play?”

Searching for mechanisms

The researchers plan to address these questions through the collaboration, designed to catalyze a new microbiome research hub at the Novartis Institutes for BioMedical Research (NIBR). The hub comprises microbiologists, immunologists, computational biologists and epithelial cell biologists, all working to understand the mechanisms by which our microbes contribute to disease. The core team will also draw on expertise from groups across NIBR, including the Natural Products Unit, where scientists have experience isolating and characterizing molecules manufactured by microbes.

“This is a dream team in terms of scientists who are excited about the microbiome,” says hub leader Leon Murphy. “We’re building a foundational understanding of the field to figure out if we should commit to it from a drug discovery perspective.”

The Novartis researchers benefit from Xavier’s knowledge of computational biology. His lab at the Broad Institute has sequenced the DNA contained in thousands of stool samples, characterizing the bacterial communities of the gut genetically and functionally. The group has published extensively on their findings. In February 2015, for example, they reported on [5] changes in the microbiome that are associated with the development of type 1 diabetes.

But Xavier isn’t satisfied with associations. He wants to figure out exactly what’s going on. While he’s managed to unravel mechanisms on his own in the past, it doesn’t hurt to have some help. Novartis has people with the skills to expedite microbiome investigations, and they sprang into action following the initial type 1 diabetes discovery.

Take Thomas Cullen, a Novartis microbiologist who happens to be an expert in bacterial membranes. He took one look at the data from Xavier’s team and came up with a hypothesis about what was happening that involved a molecule in the bacterial membrane called lipopolysaccharide (LPS). Eva d’Hennezel, a postdoctoral researcher and immunologist at Novartis, offered to test it, and in a matter of months, they had an answer—and a *Cell* paper.

“We were able to pinpoint a mechanism by which gut microbes influence the development of type 1 diabetes in newborns,” says Cullen, who is a senior author on the paper. (Xavier is the corresponding author.) “That’s the gold standard in the microbiome field.”

Diabetes driver

Here’s how the story unfolded. It’s known that children in Finland develop autoimmune diseases—including type 1 diabetes—at a much higher rate than children in Russian Karelia, despite being just next door. An international consortium of researchers has collected and analyzed samples from infants at genetic risk of developing autoimmune diseases in the two regions—which have very different standards of living—in an attempt to solve the mystery.

Xavier is leading the microbiome analysis for the consortium and his lab discovered significant differences between the microbiomes of the Finnish and Russian Karelian infants. In addition to characterizing the bacterial species present in each sample, the researchers also compared and contrasted their genes, and LPS synthesis popped out. LPS is an endotoxin that triggers an immune response. Results suggested that different bacterial species contributed to the dominant forms of LPS in the different countries.

Cullen—who was already familiar with the dominant forms of LPS—suspected that this might explain the different rates of disease. A form of LPS produced in both groups of infants is very strong, eliciting a robust immune response. A second form of LPS, one produced mostly in the Finnish infants, is much weaker and blocks the robust immune signaling of potent forms of LPS.

The weak form of LPS might be interfering with an important process in the Finnish infants: calibration of the immune system.

“Evidence is accumulating that we’re born with a highly sensitive immune system that must learn to react appropriately,” explains d’Hennezel, a co-first author on the paper. “Our microbes may play an important role in the calibration process.”

Cullen and d’Hennezel designed a series of experiments to isolate both forms of LPS from the bacteria, confirm their structural differences, and test their ability to trigger an immune response. When d’Hennezel applied the first form of LPS—produced by *E. coli* bacteria found in Finnish and Russian infants—to a variety of immune cells, the cells released many signals. When she applied the second form of LPS—produced by *Bacteroides* bacteria found only in the Finnish infants—to the immune cells, the cells were generally silent. When she administered both forms of LPS together, the second form blocked the activity of the first, keeping the cells quiet. She also tested both forms of LPS in a mouse model of diabetes, and the findings were consistent with the cellular experiments.

“With this study, we’ve built a foundation for discovering disease mechanisms together,” says Xavier, who is NIBR’s first Scholar in Residence. As such, he meets regularly with the microbiome hub, and the researchers are free to follow the science together without drafting new contracts or agreements. “We’re generating knowledge that could lead to the development of therapeutics in the future.”

Career opportunities

Find career opportunities in Oncology and Immuno-oncology research at Novartis.

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To learn more about the study, read the Broad Institute's news story [7].

In addition to being NIBR's first Scholar in Residence, Ramnik Xavier is an Institute Member of the Broad Institute of MIT and Harvard and is Chief of Gastroenterology at Massachusetts General Hospital, Kurt Isselbacher Professor of Medicine at Harvard Medical School and Co-director of the MIT Center for Microbiome Informatics and Therapeutics.

Tags:
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[2] http://www.pnas.org/content/96/25/14547.full
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