



PROFILE: RUTH LEY

Gut Reactions

A young microbial ecologist helps transform medical microbiology into a modern interdisciplinary science

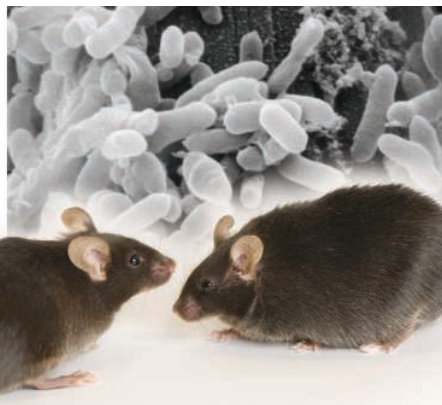
When Ruth Ley arrived at Washington University School of Medicine in St. Louis, Missouri, 5 years ago, she didn't quite know what she was getting into. "As a microbial ecologist working in a medical lab, I was a little lost," Ley recalls. She came to Jeffrey Gordon's lab because it was moving into large-scale studies of organisms inhabiting the human gut, yet she had no background in physiology or human biology. At one point, she says, a colleague in immunology asked her if she knew any biology at all.

But she turned out to be the right person in the right place at the right time. Part of a new generation of microbiologists trained in genomics, ecology, and bioinformatics, she was in a good position to help pull medical microbiology out of a long-standing rut. In that field, most research had focused on the few pathogens that could be grown in the lab and disregarded the rest. "Ecology," says David Relman, a microbiologist at Stanford University in Palo Alto, California, had "been ignored by a large subset of the more medically inclined microbiologists." Into that gap stepped Ley.

During her 4 years in St. Louis, Ley and her colleagues demonstrated that individuals vary in the repertoire of microorganisms they host—and that those variations can affect health and

disease. They discovered a link between obesity and the gut flora of mice and humans, and they traced the evolution of gut communities, showing the effects of phylogeny, diet, and other factors on the makeup of those communities. "These were foundational studies," says Martin Blaser, a physician and microbiologist at New York University, and they are helping to shape policy and scientific agendas. "She brought a very useful perspective to a group of workers who weren't thinking about [the gut] as an ecological question," adds Norman Pace, an evolutionary microbial ecologist at the University of Colorado, Boulder.

Now an assistant professor at Cornell University, Ley plans to be digging in cornfields, chasing down bacteria associated with maize roots to try to tease apart how a host's



Microbial bias. Fat and lean mice—and people—have different proportions of these *Bacteroides* bacteria (background) in their guts.

◀ **Poop search.** In barnyards and zoos, Ruth Ley seeks out interesting gut microbial communities.

genotype affects the genetic makeup of its microbial partners. That will be yet another change of environment for a scientist who has spent her professional life so far tramping through snow after alpine bacteria, sweating under the hot sun sampling microbial mats in salt ponds, and scooping up feces in the cages of lions, tigers, and bears. "What it comes down to is I'm just interested in what microbes are, and why and what are they doing," Ley explains.

Macro to micro

Ley began her scientific life as a plant community ecologist. For 3 years after graduating from the University of California, Berkeley, she worked in Hawaii for UC Berkeley's Carla D'Antonio, looking at the role of fire in paving the way for grasses to take over dry tropical woodlands on the island of Hawaii. A change in the pattern and timing of wildfires altered the nitrogen content of the soil and resulted in "a tropical woodland that turned itself into an African savanna," Ley says. Her work there sparked her interest in soils, and when she started her graduate program at the University of Colorado, Boulder, in 1995, she moved her field site from the tropics to the Rockies.

At the time, Colorado's water authorities were scratching their heads because snowmelt—the key source of municipal water—was rich in nitrogen, despite the apparent lack of much life on those high, cold peaks. Ley set up remote monitoring stations to measure environmental parameters such as temperature and nitrogen under the snow. The work revealed that the snow provided enough insulation for nitrogen-producing microbes to thrive in the soil. "Just the mass of organisms in those kinds of soils and their activity were much more than predicted," recalls her adviser, Steven Schmidt.

"At the end of my Ph.D., I became interested in what the microbes were," Ley recalls. Metagenomics was the new buzzword among microbiologists, who were using rapid sequencing technologies to decipher the DNA in entire samples of soil or water. By checking the results against databases of microbial genes, researchers

can get a handle on the diversity of invisible life the sample contained. Ley teamed up with Pace, newly arrived at the University of Colorado, to apply metagenomics to what they thought would be a fairly simple system: salt flats. She spent 3 years traveling back and forth to Baja California, battling sun and wind scraping samples from 15-centimeter-thick mats growing in meter-deep salt-works ponds. She and her colleagues dug out 15 major groups of novel bacteria.

Microbes matter

The move east to Missouri brought her into contact with yet another ecosystem: the human gut. Gordon was surveying gut communities in mice and humans and wanted to know what determined which bacteria lived where. Was it diet? Host choice? Environmental factors? And were there differences that affected how efficiently an organism processed food? Ley's experience turned out to be a perfect fit. "She comes from the perspective of studying things as a system and how they are interrelated," says Schmidt.

Gordon put Ley in charge of assessing the microbial makeup of the gut of mice carrying mutations that predisposed them to obesity. Ley and Peter Turnbaugh, a graduate student, sequenced the 16S ribosomal genes—which are often used to distinguish microbial species—from bacteria inhabiting the gut of fat mice and lean siblings lacking the mutation and compared them with what was in the public databases. They discovered that in lean mice, a group called *Bacteroidetes* predominated, but in their plump peers, the *Firmicutes* held sway; the obese animals had 50% fewer *Bacteroidetes*.

Turnbaugh transplanted microbes from both sets of mice into germ-free lean mice and watched how they grew. The ones that got microbes from obese mice "ate the same amount, had the same initial body weight and body fat, but gained more," Ley says. Gut microbes were contributing to excess girth, they reported in the 21 December 2006 issue of *Nature*, making headlines across the globe.

Once Ley started to get an inkling of the role microbes might play in obesity, she moved into the clinic, where she followed a dozen unrelated obese people on either a low-carbohydrate or a low-fat diet for a year. The exact species makeup varied from person to person, but like the obese mice, the study participants had fewer *Bacteroidetes* and more *Firmicutes* than people of regular girth; as they lost weight, the numbers

shifted in favor of the *Bacteroidetes*, Ley and colleagues reported in the same issue of *Nature*. With these studies, "she has opened very important vistas in human metabolism," says Blaser. Adds Jo Handelsman of the University of Wisconsin, Madison, the work "revolutionizes our understanding of [obesity]" and "is a model for determining [the] microbial contribution to other diseases and conditions."

Ley didn't spend all her time in St. Louis working with mice and people. She became a regular visitor to the local zoo, collecting fecal samples from as many different animals as she could. She also got samples from the San Diego Zoo and from a field biologist who provided material from 29 wild animals, for a total of 106 samples from 60 species, including 17 nonhuman primates. She tried to pick a few with diets at

odds with those of the rest of the group—such as leaf-eating colobus monkeys to contrast with their omnivore cousins, or vegetarian pandas as the outliers to fellow carnivores. She isolated and sequenced more than 20,000 16S ribosomal genes and compared those sequences with the known gut microbiota from humans, rats, cattle, and gorillas.

The flora tended to be species-specific. Pandas from the two zoos had quite similar communities, despite the geographic separation, for example. Diet also seems to have an effect: The herbivore communities tended to be more similar to each other than to communities in carnivores, and the human microbial repertoire fell squarely in line with that of other omnivore primates. "Ruth showed that there are different signatures for different types of diets," says Bryan White, a microbiologist at the University of Illinois, Urbana-Champaign. When she built a family tree to see how the microbial communities were related, the branching pattern mirrored the family trees of the animals providing the samples. The flora of brown bears and polar bears were closely related and distantly related to that of their second cousin the dog, for example. "The ancestral bear microbial community of the gut has been passed along, and you can see it," Ley explains.

Genes perspective?

Ley's work has helped drive home the close association between our microbes and ourselves. Studies of the full complement of microbial genes in and on the body—the microbiome—show that although there is quite a bit of variation from person to person, there is a core set of genes that provide essential services. In the gut, for example, those genes help break down food and make it available to the body.

Gordon thinks that because the microbes have evolved certain genes and functions, the host doesn't have to. But Ley wonders whether the reverse is also true. For example, people with high-starch diets have more copies of amylase genes than people who eat more protein have. These amylases break down starches in the gut, a function that might in certain circumstances be done by the microbes themselves. Thus variation in the numbers of copies of these genes "might have a direct impact on the genes in the microbiome or the [microbial] lineages in the gut," she suggests.

Ley plans to first attack these questions using maize stocks of known genotypes and root bacteria associated with them. Such studies should help scientists interpret results from the Human Microbiome Project, a \$115 million, 5-year effort funded by the National Institutes of Health that will sequence hundreds of human-

Widely traveled. Ley's studies have led her from tropical Hawaiian volcanoes to Rocky Mountain peaks to the dry valleys of Antarctica (top to bottom) and, ultimately, into the world of gut microbial ecology.

associated microbes and conduct surveys of the communities living in various parts of the body. The effort "needs to be more than just a description of parts," Gordon warns. The microbiome is quite dynamic, with selective forces operating on many levels shaping the diversity and functionality of these gut communities.

This push means that for microbiome researchers, "all of us are becoming ecologists," says Blaser. And that's where people like Ley come in, he adds. "It's great that we have a card-carrying ecologist to teach us."

—ELIZABETH PENNISI

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Read an "In Person" essay by Ruth Ley on dual-career couples at sciencecareers.org.

