A Bacterium's Best Friend

by Katie Neith

It's a common belief that bacteria, in general, are necessary evils—detrimental beings that live alongside us but that we should do our best to avoid. Caltech microbiologist Sarkis Mazmanian, however, is working hard to flip that script; he wants us to recognize that many bacteria are here to help and that we should be embracing them rather than trying to kill them with a barrage of soaps, pills, and sprays.

"I think that we all grew up viewing microbes as insidious little creatures that only want to make us sick—but it's simply untrue," Mazmanian says. "Making us sick doesn't necessarily help bacteria in the long run. What helps microbes most is to create an environment that's hospitable—on the skin or in the gut—for long-term propagation. If I were a bacterium, I would help my host!"

And it would be a selfish move, he points out. That's because the healthier a bacterium's host is, the better the living environment is for that bacterium. Which is why Mazmanian believes that most bacteria have, over evolutionary time, adapted to improve their hosts rather than harm them—an idea he is working to prove through his research.

The idea that our bodies are teeming with propitious microbes has been around for more than 100 years; the term probiotic—referring to a microorganism that may provide health benefits when consumed—was first coined in the 1950s.

If you look across the human population, you'll find that there are close to 10,000 species of bacteria, known as the microbiome, capable of colonizing our bodies; each of us will come in contact with some subset of that group over a lifetime. The number of bacterial pathogens that actually *infect* humans—i.e., cause harm to us—is only about 70.

And yet, Mazmanian says that when he started his work about a decade ago, he was considered to be "completely on the fringes of science" by many of his peers simply for wanting to study organisms that don't necessarily cause disease. Even today, he adds, the vast majority of scientists in the field of host-microbial interactions concentrate solely on the bugs that make us sick.

Fringe or not, however, Mazmanian's point of view has started to gain real momentum. His laboratory was the first to demonstrate that specific gut bacteria from the human microbiome direct the development of the mammalian immune system by enhancing the function of specific immune cells, and provide protection from intestinal diseases by balancing, rather than activating, the immune system. In other words, he says, fundamental aspects of health are absolutely dependent on microbial interactions with—and within—our bodies.

Mazmanian's road to radical thinking in microbiology had a rather inconspicuous start: armed with a love of writing and at the urging of teachers who thought he showed real talent, he entered UCLA as an English major in 1990.

"One of my high school teachers actually went to the trouble, without telling me, of entering a poem I had written in a national poetry contest," he recalls. "And I won first place."

But it was a required biology course—rather than one of his English classes—that caught his attention during his sophomore year in a way that nothing ever had before.

"Perhaps I was more mature than I was in high school, or the stars lined up in a way that made me appreciate it more," says Mazmanian. "But for the first time—and I can say this with a great deal of confidence—I was truly interested in a subject. That was a new feeling for me, to not just learn something but to be captivated by what I was learning. So I took a few more science classes, mostly in microbiology, and I never looked back."

He went on to get bachelor's and PhD degrees in microbiology—both from UCLA.

"I really appreciated how versatile, dynamic, and powerful these little biological machines are, and I've been a microbiologist ever since," says Mazmanian, who joined the Caltech faculty as an assistant professor in 2006 and became a full professor of biology and biological engineering in 2012.

BENEVOLENT BUGS

But Mazmanian hasn't just been *a* microbiologist since his college days; he has quickly become a leader in the field. In 2007 he was awarded a Searle Scholarship, and in 2008 was named one of *Discover* magazine's "20 Best Brains Under 40," which hailed young innovators in science. He was a 2011 recipient of a Burroughs Wellcome Fund award and, in 2012, was named a MacArthur Fellow and awarded a five-year, $500,000 "genius" grant.

Mazmanian's creative and award-garnering work on beneficial bacteria began with a simple notion. Since most symbiotic bacteria live in the intestines, he decided to start looking at the ways they might positively impact a disease in the gut—in this case, Inflammatory Bowel Disease (IBD), which includes such conditions as ulcerative colitis and Crohn's disease, and affects 1.5 million Americans and many more people worldwide. IBD is believed to start when the gut's immune system becomes activated despite the lack of an actual infection, creating chronic inflammation that

Above: A mural, painted in the second floor hallway of the Church Laboratory by a commissioned artist, illustrates segments of the human intestine where bacteria with powerful beneficial effects live.

keeps damaging gastrointestinal tissues, eventually causing such symptoms as bloating, abdominal pain, constipation, bloody diarrhea, and severe weight loss.

Mazmanian theorized that introducing "good" bacteria into a gut under siege might work to balance and thus tame this misguided immune response. So he and his team used mouse models of IBD to identify organisms that interact in a positive way with the immune system. These initial studies identified *Bacteroides fragilis*, a member of the human microbiome that produces a molecule with powerful anti-inflammatory properties, essentially stopping IBD in its tracks.

Not content to tackle only IBD, Mazmanian decided to venture beyond the gut and into the central nervous system.

"Based on both human and mouse studies, we knew that the immunological response driving multiple sclerosis was very similar to the inflammatory cascade that causes IBD," he explains. "And so we wondered if maybe beneficial microbes living in the intestines might be able to have an effect outside of the gut."

Multiple sclerosis (MS) is a neuro-inflammatory disease in which the immune system attacks the protective sheath around nerve cells, causing symptoms from tingling to numbness and even paralysis in extreme cases. As they had done in their IBD experiments, Mazmanian and his team set up cases of MS in mice, introduced *B. fragilis* bacteria into the gut and, sure enough, were able to demonstrate regulation of inflammation in the central nervous system and amelioration of the symptoms associated with MS in mice, most importantly paralysis.

"It was astonishing to see beneficial effects of the gut microbiome in tissues as distant as the brain and spinal cord," says Mazmanian.

Having looked at how gut bacteria can change and shape the immune response both in the gut and in the brain, the team is now considering how those same bacteria might affect the nervous system directly, influencing everything from neurological diseases to common behaviors. After all, Mazmanian says, the kinds of helpful molecules the microbes produced in the IBD and MS experiments are capable of interacting with any kind of cell, whether it's part of the immune system or not.

"As far as a microbe is concerned," he says, "a cell is just a cell."

To see if he could prove that point, Mazmanian began working with Paul Patterson, the Anne P. and Benjamin F. Biaggini Professor of Biological Sciences, Emeritus, a few years ago on a program to study the effect of the bacteria in our bodies on some of the behaviors seen in autism. Why autism? For one thing, Patterson had recently modeled autism in a mouse and reproduced many of the features of the disorder in humans, including the so-called leaky gut issues that many children with autism experience. He and Mazmanian then introduced probiotics—again, *B. fragilis*—into the bellies of the animals to see what influence the bugs might have on the GI problems as well as specific behavioral symptoms.

They recently reported their results in the journal *Cell*, noting that the probiotic-treated mice showed fewer signs of anxiety, were less likely to engage in a repetitive behavior, and were more likely to communicate with other mice than their untreated counterparts. Anxiety, repetitive behavior, and defects in communication are hallmarks of autism. Mazmanian thinks these changes may be thanks to the microbiome's regulation of the release of certain metabolites involved in developmental functions.

"We've been working for several years on exactly what these mechanisms are and how commensal microbes interact with other microbes in the gut, how they interact with the gut's epithelial cells, how they interact with the gut's immune cells, and how they interact with the nervous system, all in the context of autism," he says.

The ultimate goal of his research, Mazmanian notes, is the development of therapeutic probiotics—pills containing helpful organisms that would colonize your gut and keep you healthy. Such pills would be used to address more than just IBD or MS or autism; they could, Mazmanian says, be useful in both protecting against and reducing a wide variety of symptoms and conditions associated with the immune, nervous, and metabolic systems.

"We describe our efforts as discovery of 'drugs from bugs,'" he says.

So why not just grab some of the commercially developed probiotics on the market today? While there are certainly plenty to choose from, Mazmanian says, there is little to no evidence that they provide any real benefit when tested in clinical trials. After all, the bacteria in the probiotics available at your local health-food store were chosen for their long shelf life rather than for benefits shown through medical research. And while Mazmanian expects that probiotics based on his studies will be in clinical trials within the next two years, he knows that the natural course of drug development takes time; he says it's likely to be at least a decade before these probiotics become available at your local pharmacy.

In the meantime, Mazmanian says, the best thing we can do to keep ourselves healthy and to give ourselves the benefits offered by the obliging microbes already in our bodies is to stop using antimicrobial agents and reduce high-fat, high-sugar diets. He points out that in Western societies—where antibiotics, sanitation, and the use of antibacterial products are the norm—rates of IBD, MS, and autism are increasing rapidly. The "cleaner" we live, it seems, the more likely we are to increase our risk of developing these kinds of immunologic and neurologic disorders. He also notes that the "Western diet" alters the microbiome, which may impact the effects of gut bacteria on the immune and nervous systems.

Modern lifestyles include strategies that have led to critical advances in controlling infectious disease. However, "in our efforts to distance ourselves from infection, we've also altered our association with beneficial organisms," Mazmanian says. "I think evidence is mounting that the absence of microbes may well be a risk factor for certain diseases.

A HELPING HAND

Mazmanian's beneficial bacteria aren't just improving health; they're also helping to advance science in Armenia. Or, at least, they're helping to fund that advancement of science. When he isn't testing the effects of beneficial bacteria in the lab or helping the young scientists he mentors develop into independent thinkers—something he calls his "greatest joy"—he is using the funds from his MacArthur grant to help provide aid to the Armenian scientific community.

"When you go to developing countries and see the conditions by which other people are trying to do science, it's night and day compared with the standards we enjoy in the United States," says Mazmanian. "I'm Armenian—if I didn't use the opportunity as a successful scientist to help bourgeoning scientists in Armenia, then I wouldn't be using my very fortunate position to its fullest."

So, beginning in 2008, Mazmanian worked to build a relationship with scientists and university administrators in Armenia. These days, Mazmanian and three additional scientists he's recruited from different U.S. institutions head to the Molecular Biology Institute in Yerevan, Armenia, each fall, where they spend a week teaching 50 to 60 graduate and medical students about the ways humans and microbes affect and shape one another's lives.

"It's really a small contribution in the grand scheme of things, because there's only so much you can do in one week," Mazmanian says. "I leave once the course is over, and for 51 weeks they go back to very poor conditions—it's like a Band-Aid on a festering wound."

The way to really begin to close the wound, he says, would be to build—from the ground up—a research institute in Armenia that is based on the scientific approaches and technologies being used in the United States, Europe, and Japan—the world's leaders in scientific discovery. That, he says, would be a true benefit to the people of Armenia.

"Whether or not this will happen, I'm not sure," says Mazmanian. "But it's my dream. If it comes to pass, I think it could be the most impactful thing I will ever do as a scientist."

He is quick to point out, however, that for any gains he makes in Armenia, he has countless people to thank back in the States. Without the successes of his research lab, none of his extracurricular work would be possible.

"So many students and research fellows have given abundant time, energy, and intellect to help move forward our lab's contribution to science and society," Mazmanian says. "Their hard work has put me in a position to help others."

And though he hasn't done creative writing in many years, Mazmanian doesn't hesitate to wax poetic about his and his team's ultimate ambitions to change the public's view of bacteria into a more positive sentiment.

"If our bodies are colonized with microbes not making us sick, there is no room or space for invaders," he stresses. "For example, if you have lush vegetation, weeds don't grow. But if all the plants die off, the weeds come because there is room for them. The microbes that live inside and on us actually help us fight off infections, they improve our immune and nervous systems, and our lives. If we embrace them as old friends and not as new enemies, then we may appreciate and potentially harness the awesome power of bacteria as revolutionary therapies for people suffering from various diseases, both in the U.S. and abroad." E&S

Sarkis Mazmanian is a professor of biology and biological engineering. His research is funded by Caltech, the National Institutes of Health, the Crohn's and Colitis Foundation, the Department of Defense, Autism Speaks, and several other charitable organizations.