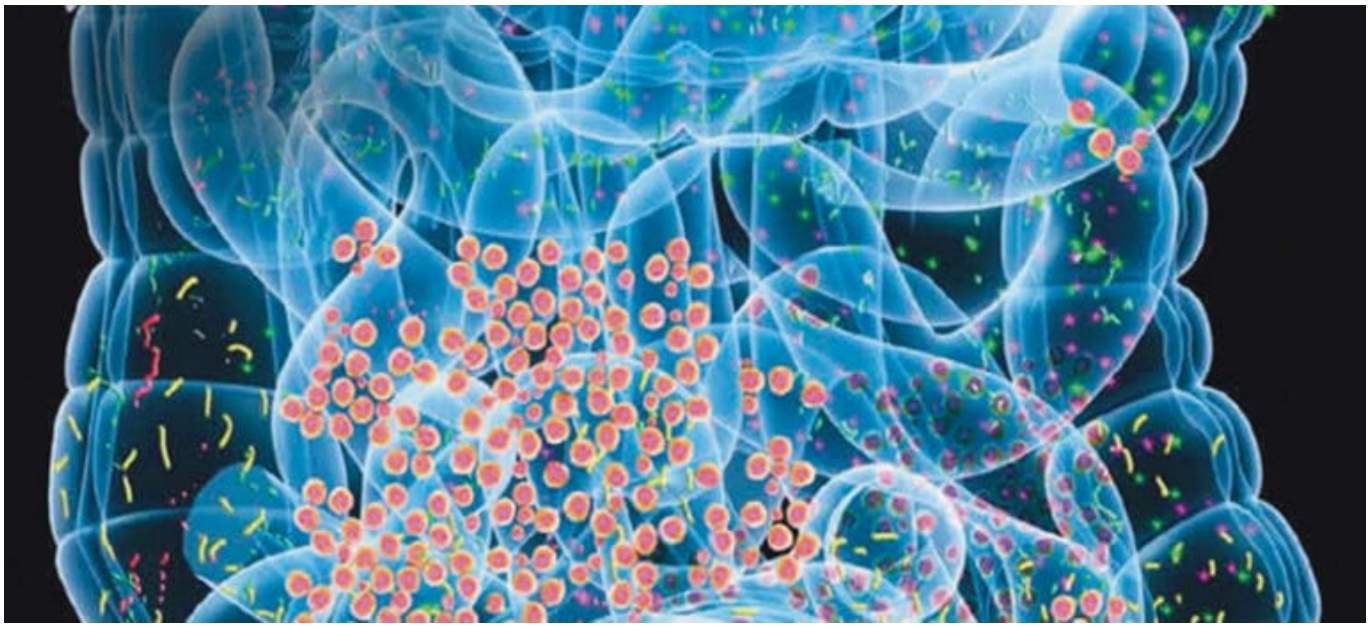
Gut check



An update on microbiome research in multiple sclerosis and an in-depth look at the work the iMSMS is doing.

by Mary E. King, PhD

How do the bacteria that live in our gut affect the development and progression of multiple sclerosis? Sergio Baranzini, PhD, professor at the Weill Institute for Neuroscience at the University of California in San Francisco, is a founding member of the International Multiple Sclerosis Microbiome Study (iMSMS), a consortium of researchers that aims to answer this important question with a large study of the same name. Baranzini provides an update on the field of gut microbiome research in MS and an in-depth look at the work the iMSMS is doing.

Why the interest in gut bacteria?
"We harbor as many bacteria cells in and on our body as our total number of human cells; that is, we are only about 50% human!" Baranzini stresses. So far, he explains, researchers looking for MS risk factors have focused on the human genome, which includes about 25,000 genes. However, the gut microbiome, which contains all the genomes of all bacteria that reside there, includes about 1 million genes, far outnumbering our human gene pool. "What brought me into MS microbiome research from my background in human genetics is that we now know these bacterial genomes are tremendously diverse," he says. "The fact that they code for so many times more genes than our human cells was surprising and exciting to me."

Previous research has shown that human gut bacteria definitely affect mouse models of MS (called EAE). For example, Baranzini demonstrated that transplanting gut bacteria isolated from individuals with MS into mice raised in germ-free conditions produces worse EAE than using bacteria isolated from healthy individuals.

But how do bacteria from the gut affect the immune system and immune diseases like MS? "We know that the immune system comes into close contact with our intestinal flora in the gut where the immune system is affected — 'educated' — by the molecules that are released from these bacteria," Baranzini explains. "We need to know what triggers MS, what exacerbates MS, and what perpetuates MS, and we think gut microorganisms play an important role in these processes." We also have different bacteria in our guts in response to factors, such as our diet or whether we live in the countryside or an urban setting. Baranzini points out that this means our immune systems are being affected by these very same external factors through the changes they induce in our gut microbiomes.

What is the iMSMS and what does it aim to do?
"Our research organization was created in 2013 as a small U.S.-based group, called the MS Microbiome Consortium, thanks in large part to funding from the National MS Society," Baranzini says. "This Society program specifically awarded us money to start a new collaboration in MS research that otherwise wouldn't happen. It stipulated that we include key researchers from outside the field of MS who could help spark new ideas and approaches among the group members."

Society funding allowed the organizers to bring together experts in MS genomics, clinical care and research, neuroscience, microbiology and cutting-edge methods for identifying massive numbers of microbial species. "That was the beginning," Baranzini says. "Without Society support, we couldn't have obtained the preliminary data that enabled us to get further funding. We have now expanded to 12 research groups at 10 sites in North America, Europe and South America, and as our group expanded, we adopted the new name, International MS Microbiome Consortium."
The iMSMS objective is to recruit 2,000 patients worldwide and identify and sequence the DNA of their gut bacteria to create the largest microbiome study ever done in MS. "We are hoping this will be THE reference study for this subject and that our data and conclusions will stand for years to come," Baranzini says.

The iMSMS plan
The iMSMS has two main goals.

1. To establish a reference map of gut microbiome DNA in MS. "That's why we are doing this large DNA sequencing project," Baranzini explains.
2. To understand the role that the gut bacteria play in MS.

He says iMSMS scientists are already making progress by taking certain specific bacteria that are present in stool samples from patients with MS and growing them with immune cells in the lab. This allows researchers to see how the immune cells are affected and may eventually help explain why and how some particular differences in gut bacteria influence MS.
Baranzini explains that it is difficult to control for environmental factors like diet or location when trying to compare the effects of the microbiome on a specific research question in MS. The iMSMS came up with a clever solution as part of the study design. The research sites are

recruiting household pairs, a person with MS and the person's spouse or roommate, which provides a natural, matched control subject for each person with MS.

Researchers collect stool and blood from each participant. The different species of bacteria found in stool have distinguishing features in their DNA that can be identified by special types of laboratory techniques called DNA sequencing. Investigators purify DNA from bacteria isolated from stool samples and analyze it to determine which bacteria are present. (Some human cells are shed into the stool, and the gut also contains some fungi and other microorganisms, but 99% of the DNA will be from bacteria.)

The iMSMS is recruiting participants and collecting samples in a very rigorous and standardized way, "unlike many studies we and others have undertaken previously," Baranzini states. "We are about halfway to our recruitment goal, which is exciting, but we need another two to three years to complete recruitment."

Hoping to translate research to treatment

"There is a lot to be discovered in how gut bacteria modify a person's response to MS treatment as well as how they affect the availability of a treatment inside the body, especially oral medications," Baranzini says. He points out that cancer researchers have shown that the type of bacteria present in a patient's gut can affect the response to a specific therapy. So it was natural to look at this question in people with MS, too.

Consortium researchers compared two groups of people with relapsing-remitting MS treated with different disease-modifying therapies (DMTs) and identified differences in the compositions of the gut microbiomes in the two DMT groups compared with the control group, known as the treatment-naïve group. These changes affected important pathways that alter vitamin, amino acid, energy and drug metabolism. This was just a first step in understanding the complex issues of interplay between the microbiome and treatment, Baranzini explains. The results underscore the need for more investigation in a large, well-controlled study.

Preliminary results from the first 256 participants (128 with MS and 128 controls) in the current large reference study were presented at the September 2019 meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

Can probiotics help?

Baranzini says that he is often asked about probiotics (such as yogurt or supplements) and whether he can make any recommendations about them for people with MS. "Unfortunately, there is no strong evidence so far that any probiotics have any effect on MS. In the iMSMS we are recording probiotics as well as food intake, over-the-counter and prescription medications, supplements, etc. We hope to learn whether a certain probiotic has any effect on gut bacteria in individuals with MS and whether this has any positive or negative impact on the disease," he explains.

Additional iMSMS results will be available in 2020. Full study results will take longer because recruiting participants and doing the laboratory analyses are time-consuming. Baranzini is sympathetic to people with MS who need and want answers as soon as possible. “I understand the urgency of patients in understanding this question, and hopefully we will see new progress within the coming decade. Getting good, reliable answers takes large, responsible studies that then need to be verified. Unfortunately scientific progress proceeds at a slower pace than we would like,“ he says.

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