NEWS

Taking Stock of the Human Microbiome and Disease

Programs that helped jump-start the microbiome field have yet to come up with the best way to follow up on their discoveries

PARIS—We are not alone. Our bodies, inside and out, are teeming with trillions of microbes. Most of them are our friends, helping us to digest food, strengthen our immune systems, and keep dangerous enemy pathogens from invading our tissues and organs.

Evidence is building that this resident community of microbes, called the microbiome, plays a major role in health and disease. “We humans co-evolved with our microbial communities,” says Lita Proctor, a microbial ecologist and program director of the Human Microbiome Project (HMP), a special project of the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, that has spent \$170 million over the past 5 years to catalyze microbiome research. “It is this co-evolved relationship that has expanded our capabilities beyond what is coded in our genomes to defend against disease, adapt to new environments, exploit a diverse diet, and thrive as a species.”

But when the normal composition of the microbiome is thrown off balance, research-

ers say, the human host can get into serious trouble—especially because the 5 million to 8 million different microbial genes in our bodies vastly outnumber the 20,000 or so human genes. Indeed, recent research has implicated microbiome imbalances in disorders as diverse as cancer, obesity, inflammatory bowel disease, psoriasis, asthma, and possibly even autism (*Science*, 26 November 2010, p. 1168; 1 April 2011, p. 32).

HMP, together with a European program called Metagenomics of the Human Intestinal Tract (MetaHIT) and government agencies in France, Japan, Canada, and other countries, have provided a major boost to microbiome research over the past several years. But HMP and MetaHIT are now coming to a formal end this year, and the follow-on efforts are still unclear. The real challenge is to establish cause and effect between the microbiome and health. At issue is whether it's best to tackle that challenge with a top-down approach, investigator-initiated proposals, or a combination of both. Scientists

are also grappling with some of the social and ethical issues related to microbiome research, including concerns that exaggerated claims for so-called probiotic products that can alter the microbiome—many of which are already on the retail market—could discredit the field.

Gathering steam

Microbiome research didn't start with HMP and MetaHIT, but those programs did help in “raising visibility and attracting a much larger number of people to the field,” says David Relman, a microbiologist at Stanford University in Palo Alto, California, who has worked on the microbiome for at least 15 years. When he started, he and others lacked good tools to identify the microbes teeming in the human gut, skin, mouth, nose, and reproductive tract. Since then, there has been “tremendous progress,” says S. Dusko Ehrlich, a molecular biologist at the French research agency INRA and coordinator of MetaHIT. New methods have made possible the characterization of our flora. Those methods include high-throughput DNA sequencing; effective, relatively low-cost techniques that allow the cataloging of millions of sequences at a time; and the identification of bacterial species without having to culture them—largely by using a short segment of their ribosomal RNA called 16S rRNA as a taxonomic marker.

Over the past 4 years, for example, MetaHIT's scientists carried out a sequencing study on 124 subjects from Denmark and Spain and found a total of at least 1000 different bacterial species that inhabit the gut, with each subject harboring an average of 160 species. All told, the researchers have come up with 3.3 million genes in the gut alone and have proposed that people have one of three “enterotypes,” microbiomes dominated by a particular bacterial genus.

HMP-funded researchers, meanwhile, have sequenced more than 2000 microbial genomes, with a total goal of 3000 genomes, creating a reference database that will allow scientists to more rapidly sequence and assemble microbial genomes taken from human and animal subjects. And in studies involving about 300 volunteers, HMP researchers have decoded microbial genomes found in the gut, mouth, nose, skin, and reproductive tract, providing a detailed picture of how the microbiome differs between individuals and body sites. Other projects investigated the role of the microbiome in diseases affecting the gut, reproductive tract, and skin.

What next

One big question for the future is whether to stress gathering more data on healthy and unhealthy microbiomes or focus on establishing causal relationships between the microbiome and disease. Indeed, Proctor says that intense discussions are now under way within NIH and between the agency and microbiome researchers over HMP's future.

Microbiome scientists told *Science* that they want to see continued development of computational genomics. Both MetaHIT and HMP have pushed for new databases, mathematical algorithms, modeling approaches, and software packages. But more tools are necessary to take the effort "to the next level," as Relman puts it, which would include functional studies to determine more precisely what role the microbiome is playing in various diseases. Indeed, this past March at the International Human Microbiome Congress held here, Proctor said a prospective "HMP2" would likely concentrate on developing new bioinformatics and computational tools, as well as expanding mouse and other animal models to investigate whether changes in microbiome composition are the cause or effect of disease states.

But others think that more ambitious approaches are necessary. Rob Knight, an evolutionary biologist at the University of Colorado, Boulder, says he would also like to see "a targeted effort to characterize the diversity of the microbiome in different populations," similar to how the Human Genome Diversity Project collected DNA from indigenous populations (*Science*, 10 June 2005, p. 1554). And Relman says that an HMP2 could mount a microbiome version of the famous Framingham Heart Study by following thousands of people from birth for at least 20 years to see how their microbiomes fluctuate over time and correlate with disease states.

At issue, too, is how microbiome research should be funded. Knight, for example, advocates a boost in funding of two to five times the \$170 million that HMP spent over the past 5 years. But Relman worries that if too much money is allocated to the kind of centralized and "top-down" approach represented by HMP, "we will end up with limited resources for grassroots, investigator-initiated proposals."

Proctor agrees that funding such independent work should be the ultimate goal but thinks that microbiome research still needs a targeted approach for now. "The real success in human microbiome research will be when we no longer need standalone

Microbial connection?
Future studies should help clarify how the microbiome contributes to obesity.

programs in human microbiome science," she says. Nevertheless, Proctor argues, the catalytic role of HMP has already led to an increase in total microbiome spending far beyond what Knight advocates. "We estimate that there has been an eightfold increase in microbiome funding across all NIH institutes," excluding HMP funding itself, since HMP's inception.

Meanwhile, the European Commission is expected to put out a call for new microbiome proposals in July, Ehrlich says. A draft proposal now circulating suggests that the commission would fund more targeted research

Even before the commission commits, France is putting its weight behind microbiome efforts. It will provide \$25 million for the 10-year, \$104 million MetaGenoPolis, which will create a biobank of up to 1 million stool samples and expand gene profiling and high-throughput gene screening of the microbiome. The goal, says Ehrlich, the coordinator, is "to speed connecting microbiota to health and disease and open avenues for interventions."

Clouds on the horizon

Although the future seems bright for microbiome research funding, there are some practical concerns. At the Paris meeting, Richard Sharp, director of bioethics research at the Cleveland Clinic in Ohio, warned that the U.S. Food and Drug Administration was

likely to be hesitant about microbiome clinical trials. Regulation "could become a major roadblock," he says.

Sharp also advocated that microbiome researchers do more public outreach to counter the often "grossly misleading" statements made by some companies that sell probiotic products designed to alter the microbiome. This merchandise is widely available in health food stores and via Internet retailers. Knight agrees that this is a "huge problem. ... Public enthusiasm for probiotics greatly outstrips current evidence, even if the potential is very high."

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BAYLOR COLLEGE OF MEDICINE

than before, including the analysis of differences in microbiome profiles between different populations, a focus on autoimmune and inflammatory diseases, and ways to restore the microbiome after it is disrupted by antibiotics or other treatments. The proposal also calls for giving priority to projects that involve industrial partners.

Over the past 4 years, the commission contributed nearly \$15 million to MetaHIT, and this was matched by a nearly equal amount from both public and private sources. The new plan could boost the European Commission's share alone to nearly \$40 million.

He and others say that the promise of interventions that can modulate and modify the microbes that we coexist with makes the field particularly important and attractive. Says Proctor: "Unlike the human genome, the microbiome is changeable, and it is this changeability which holds real promise." Kjersti Aagaard, an obstetrician-gynecologist and microbiome researcher at Baylor College of Medicine in Houston, Texas, agrees: "My hope is that this will be one of the most rapid translations from [lab] bench to bedside seen to date."

—MICHAEL BALTER