SPOTLIGHT ON MICROBIOLOGY

Microbiology gets bigger

Gut bacterial studies open up new doors for medicine, and collaboration opportunities for researchers.

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ONCE, A microbiologist would spend their time studying individual species of bacteria one by one. Now, microbiologists look at how those bacteria and their hundreds of thousands of genes work together — with the immune system, metabolic pathways, and even with the brain.

An accounting of the millions of genes in the human gut — collectively known as the human microbiome — was recorded over the past decade by several large sequencing efforts including the Human Microbiome Project in the US and MetaHIT in Europe.

The research found that, for every single gene we hold in each cell, the collective bacteria in our gut accounts for around 20.

The two projects have expanded and energized microbiology research, as each of the thousands of bacterial species in the gut need detailed analysis of their own. Additionally, the sheer size and complexity of the data is drawing other disciplines into microbiology — including bioinformaticians, systems biologists, synthetic biologists and even ecologists.

Opportunities in microbiology are now appearing on two fronts. Since the publication of the microbiome, many universities have launched multidisciplinary centres that aim to study gut bacteria and how they interact with the human body. Also, because of a growing awareness of the role these bacteria play in diseases, drug discovery companies are hustling to harness the microbiome's therapeutic potential (see **bang or bust**). If that potential is realized, microbiome-based medicine could create an entire new therapeutic arm, alongside small molecule medicines and protein-based therapies.

New microbiome research centres — at New York University, the University of Pennsylvania, the University of California, San Diego, the Massachusetts Institute of Technology, and many others — have opened their doors in the past five years. All are adding multidisciplinary faculty to their ranks — not just microbiologists.

In Europe, Imperial College London launched the Centre for Digestive and Gut Health in 2011. King's College London followed suit with British Gut — an open-source effort to study microbial diversity — in 2014. And in January this year, the Karolinska Institute in Stockholm, Sweden partnered with Ferring Pharmaceuticals in Switzerland to build a new therapy-focused microbiome research program.

New journals are also being devoted to this area, including *npj Biofilms and Microbiomes*, which published its first issue in March 2015.

Stanford University launched the Center for Human Microbiome Studies this March. As co-director, Justin Sonnenburg aims to get a grasp on the microbiome's size and complexity by changing the microbiome of humans and watching how this affects other aspects of their biology. Because there are trillions of microbes in our gut, representing thousands of species, this will not be easy. Microbes interact both with each other and with our bodies. Further complicating things, they are not static. The population can change, due to diet or antibiotics. Species can die off or evolve.

Sonnenburg suspects that opportunities for scientists willing to engage in microbiology will grow. For instance, he's looking for a postdoc who can mine data related to the immune system and the microbiome to build mathematical models for medical predictions. Such a person must be familiar with both immunology and microbiology, of course, and must have a strong computational background.

But, once a scientist meeting that description conducts bioinformatics analysis, the

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lab will still need to check how the modelled interactions can be translated to humans, and understand the underlying mechanisms. "You still have to roll your sleeves up and do experiments," Sonnenburg says.

Heidi Nelson, director of the Mayo Clinic's four-year-old Microbiome Program, based at the Rochester, Minnesota hospital, is also looking for someone to build mathematical models out of microbiome research, though she says her biggest need is in systems biology. The models will help clinicians narrow their therapeutic approaches, and also develop treatments for individual patients. Patients' microbiomes vary, depending on diet and disease.

To inform the clinician, Nelson sees more fields and specialties developing that could help doctors understand which microbial genes contribute to diseases, including drug-resistant infections. "Somebody's going to have to be the bridge to clinical practice."

Nelson agrees with Sonnenburg that microbiome data creates an intersection between immunology and microbiology, because many chronic diseases — like Crohn's and Inflammatory Bowel Disease (IBD) — result from inflammation and microbial imbalance in the gut. But she sees another disciplinary crossroad: metabolism. The gut bacteria, both individually and collectively — create molecular compounds that help maintain gut health and function. But when the balance is altered, diseases emerge. Therefore, scientists who can apply high-throughput screening of metabolite production to the microbiome should be in great demand.

Tim Spector, a professor of genetic epidemiology at Kings College London, is more interested in how microbiomes interact with dietary variations, rather than mining the gut for medicine. He estimates that humans only share about 20 percent of their microbiome universally. That makes identifying simple variants for broad treatment tricky. "We mustn't underestimate the complexity of the microbiome," Spector says.

Still, there are some broad patterns. Diets rich in fruits, vegetables and unprocessed grains tend to produce the most robust microbiome, in terms of diversity. A more Western diet of meats, fats and processed foods tends to produce a less diverse microbiome.

To help bridge academic research with clinical approaches, the Janssen Pharmaceutical Company — a subsidiary of pharma giant Johnson & Johnson — created the Janssen Human Microbiome Institute in 2015. They named Dirk Gevers, a computational biologist and formerly a group leader at the Broad Institute, to run it.

He is eager to learn how the gut bacteria function collectively. "The next generation of microbiology is not about individual organisms on their own, but about understanding how organisms in the community are interacting with one another and with the host," Gevers says. As a result, he sees microbial ecology as an emerging field. The idea is to look at the gut as a rainforest, with a robust amount of species living together. Adding or subtracting some species may have small effects, while altering populations of others could have drastic consequences.

Gaining an ecological understanding of this system has the potential for treating diseases at their root, rather than just dampening their symptoms. For example, existing therapies for IBD just silence the immune system once the disease has kicked in and caused inflammation. A complementary approach could arise from understanding which microbes are causing the inflammation, then adjusting their populations accordingly.

Because the microbiome impacts so many biological systems and harnessing it has so much therapeutic potential, Gevers suspects scientists from many backgrounds will play a role in studying it. "This entire field is looking for talent, whether your background is in the wet lab, as a computational biologist, or if you're in drug development — you are highly sought after to start work at institutions that are building interdisciplinary microbiome centres," Gevers says.

Dirk Gevers

Roger Pomerantz, chief executive of Seres Bioscience, agrees with Gevers' rainforest analogy, although he prefers a coral reef one. That philosophy has coloured the company's approach to drug development. They are testing a cocktail of bacteria that, they hope, could "reseed" the human microbiome after several waves of antibiotics have wiped out key bacteria in the gut. They have confidence in this approach, because some people who've experienced Clostridium difficile infection following antibiotics have been treated by repopulating gut bacteria through a faecal transplant from a person with a healthy microbiome. Seres aims to replace only key bacteria, in capsule form, rather than the entire microbiome in a faecal transplant. If successful, they intend to move on to IBD and Crohn's as well.

And, now that Seres have multiple candidates in clinical studies, they are seeking people with commercialization skills, such as marketing and regulatory affairs. If Seres — and a growing number of biotechs tapping into the microbiome — succeed, it could lead to more such jobs, as well as a continued growth in microbiology research that overlaps with immunology, metabolism and other disciplines.

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Bang or bust

The human microbiome is at a juncture.

The ability to harness the thousands of bacterial species in the human gut to treat illnesses ranging from Crohn's Disease to cancer could be the next biotech revolution — creating a whole new branch of therapeutics, next to small molecules and biologics. Or, it could be the next gene therapy: a vastly overhyped field that hit a wall, and is only now making incremental impacts.

Microbiome-based start-ups — and the Pharma firms and venture capitalists funding them — think it's the first. They've pumped millions of dollars into scores of companies, many of which have ramped up hiring as their therapies progress through clinical trials. Will these investments pay off? The next few years should provide the answer. If early candidates clear clinical trials and make it to market, investments will continue and job growth will skyrocket. If not, the field will retrench. The science is sound — the question is whether clinicians, and the companies funding them, are able to exploit the microbiome for practical therapies.

Karim Dabbagh, CSO of Second Genome, in South San Francisco, says the field is "exploding," because the microbiome impacts so many areas — nutrition, diagnostics, agriculture, as well as medicine. The company has collaborated with Johnson & Johnson, Pfizer, the Mayo Clinic and Cork University in Ireland to explore some of these relationships, and raised $42.6 million in April.

Dabbagh says that faecal transplant successes showed proof of concept. Dabbagh and others also add that, unlike small molecules from pharma or biologics in biotech, microbiome-based therapies aim to utilize molecules natural to the human body. That should, in principle, increase safety, if not guarantee efficacy. And if both are proved in clinical trials, investment and jobs will increase, he says. "This definitely feels like the early days of biotechnology and recombinant DNA."