Human microbiome: Boon or boondoggle for drugmakers?

By Marie Powers, Staff Writer

SAN DIEGO – Although research about the human microbiome is in its infancy, the science is advancing rapidly, with observations about the microbiome signature in various disease states reported almost weekly in peer-reviewed journals. Carefully designed cause-and-effect experiments also are being conducted, and the findings are turning the heads of venture capitalists and big pharma. But the space is so large and unwieldy and the regulatory pathway so new that efforts to capitalize on the beneficial microorganisms that colonize the human body threaten to overwhelm small biotechs seeking to build drug discovery platforms.

Certainly, interest is high. In one of the last presentations on the final day of the BIO International Convention, a panel discussing the opportunities and challenges in microbiome modulators drew a standing-room-only crowd. It was clear from the tenor of the discussion among an audience of venture capitalists, pharmas and practicing clinicians, however, that the topic still generates more questions than answers.

Executives at companies exploring the space caution that novel drugs designed to exploit gut microbes are not just around the corner. Instead, those companies are probing the mechanistic link between the microbiome and human disease and using first principles to attack known pathogens.

Cubist Pharmaceuticals Inc. is among the leaders showing mettle in that battle. Last month, the company reported at the 24th European Congress of Clinical Microbiology and Infectious Diseases in Barcelona, Spain, that its ceftolozane/tazobactam combo antibiotic, known as CXA-201, demonstrated microbiological eradication of key problematic gram-negative pathogens, including Pseudomonas aeruginosa and extended-spectrum beta-lactamase producing E. coli and Klebsiella, in a phase III study in complicated urinary tract infections and complicated intraabdominal infections. (See BioWorld Today, May 13, 2014.)

Earlier this month, the FDA accepted the company’s new drug application covering both indications for priority review. Cubist plans to file with the EMA in the second half of the year.

This month, the FDA also approved Cubist’s once-daily oxazolidinone antibiotic, Sivextro (tedizolid phosphate), to treat certain gram-positive bacterial infections, including methicillinresistant Staphylococcus aureus. That drug was picked up in Cubist’s $704 million acquisition of Trius Therapeutics Inc. in 2013. (See BioWorld Today, July 31, 2013, and June 24, 2014.)

In addition, Cubist markets Dificid (fidaxomicin) in Clostridium difficile-associated diarrhea (CDAD) and has its own candidate, surotomycin (formerly CB-183,315), in phase III studies in the indication. (See BioWorld Today, Sept. 30, 2011.)

Steve Gilman, executive vice president of research and development and chief scientific officer, told the BIO audience that narrow-spectrum surotomycin has shown comparable efficacy to vancomycin in CDAD without the destructive effect of vancomycin on the gut flora – a key differentiator in taking the drug forward.

Still, Gilman acknowledged that big phamas are just starting to show interest in the human microbiome. Companies that place big bets early could get burned if the field moves in a different direction or the
technology doesn’t work as advertised, but “we’re getting close to something popping in this area in the next five years,” he predicted.

**Asking why, how the microbiome works**

In fact, the pharma partnering door to the human microbiome already is propped open. In 2013, Second Genome Inc. inked a deal with the Johnson & Johnson Innovation Center and Janssen Research & Development LLC to discover drugs for ulcerative colitis. (See *BioWorld Today*, June 6, 2013.)

Second Genome followed that up last month with a partnership with New York-based Pfizer Inc. on a large observational study exploring the relationship among the microorganisms that comprise the human microbiome and obesity and metabolic disorders. (See *BioWorld Today*, May 2, 2014.)

The South San Francisco-based firm didn’t disclose terms for either agreement, but Mohan Iyer, Second Genome’s chief business officer, told *BioWorld Insight* at BIO that the transactions indicated pharma’s growing appetite for that type of technology. Increasingly sophisticated experiments are showing that “the microbiome is a critical player in health and wellness, and that has changed the mindset of the large pharma companies,” he said.

Interest in the microbiome isn’t limited to drug development. Additional opportunities include biomarkers, diagnostics and nutraceuticals. The vast potential of the microbiome forces small companies to decide fairly quickly what strategy they intend to pursue.

“At Second Genome, we’ve taken a view that we want to understand the mechanistic link of how the microbiome modulates disease,” Iyer explained. “How does it play a role in disease, and how can we think through actionable mechanisms that we can drug? That is the key that opens up pharma interest.”

As a small, venture-backed firm, Second Genome made “a conscious decision” to go directly into building a drug discovery platform rather than moving in that direction as an end game.

“We’re asking why the microbiome works, and how it works,” Iyer explained. “To answer those questions, you need a whole bunch of different tools. You need to build an entirely new platform that’s a mix of genomics technology, in vitro assays for function and in vivo tools. Building that platform is what has drawn the pharma interest.”

Paris-based Enterome Bioscience SA, on the other hand, is starting with the development of biomarkers for gut microbiotarelated diseases, with a long-term plan of translating that scientific understanding into therapeutics. Last month, the company raised €10 million (US$13.9 million) in a first closing of a planned €20 million series B round for further development of its microbiome-based biomarkers. (See *BioWorld Today*, May 2, 2014.)

“When building a house, you need to think first about the foundation,” said Pierre Belichard, the company’s CEO, who spoke at BIO. “You need to understand the relationship between the gut composition and the disease. We are currently developing a number of biomarkers. The next challenge will be to develop new drugs on the basis of the interplay between the gut and disease.”

**Defining ‘normal, healthy’ an important task**
Roseville, Minn.-based Rebiotix Inc. is another believer in the broad potential of the microbiome. Initially, the company also is targeting CDAD, which Lee Jones, the company’s president and CEO, called “a small piece of a big pie.” The company chose CDAD as its first indication based on the medical need and on research suggesting that fecal transplants – the predecessor therapy to its microbiota restoration therapy – showed clinical benefit in related conditions. (See *BioWorld Today*, Sept. 30, 2013.)

The microbiome “is not just a research project,” Jones told *BioWorld Insight*. “Nobody really knows what works today – why you can put a bunch of live microbes in somebody and see a change in their disease or condition. We’re seeing the really early, early stages of development. But as people get a better understanding of the technology, it wouldn’t surprise me to have a drug discovery program that ends up looking more like a conventional pharmaceutical than a microbial mix.”

Still, the field remains populated with unanswered questions.

“One point that’s critical to address is how to define a healthy microbiota,” observed David Martin Jr., chairman and CEO of South San Francisco-based Avidbiotics Corp., who was a BIO panelist. “Are you going to define it by the microbiome – by which genes are present? Or are you going to define it from a biochemical standpoint? Knowing what’s normal and healthy is going to be a difficult but important chore. Until we know that, we can’t anticipate what the issues are going to be and how to prevent disease that’s a consequence of what’s going on in the gut.”

**‘In every disease, there’s going to be a revelation’**

Once those secrets are unlocked, many in the field predict a rapid trajectory in drug discovery, initially targeting gastrointestinal diseases such as Crohn’s and inflammatory bowel disease as well as metabolic targets.

Most eventually expect scientists to identify a link between the microbiome and virtually every therapeutic area. In oncology, early reports already suggest that responses to major chemotherapeutic drugs are modulated by the microbiome, according to Iyer.

“In every disease, there’s going to be a revelation,” he said, adding that “clear relationships are starting to form” between the microbiome and central nervous system diseases such as multiple sclerosis and autism. Additional studies are focusing on the association between the microbiome and skin diseases such as psoriasis and atopic dermatitis as well as respiratory ailments such as asthma.

“It’s not causation,” Iyer said. “But we can see that the microbiome is relevant. If we can move that relevance from a correlative event to a causative event and understand the mechanisms of each, we can build a platform that can go across those therapeutic areas.”

Martin said the microbiome ultimately could provide the platform to develop drugs that act as “snipers” against disease, attacking with laser-like precision, rather than continuing the shotgun approach of conventional antibiotics that breed resistance. But that, he conceded, is not a popular approach with big pharma.

“Pharma wants broad-spectrum, which is a marketing decision, because narrow-spectrum won’t be a billion-dollar drug,” he said. “What we really need, instead, are broad-spectrum diagnostics and very narrow-spectrum agents to kill the harmful organisms identified.”