"The Pink Sheet"

Big Pharma Embraces Microbiome Research; Partnering Poised To Follow

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The Pink Sheet

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Executive Summary

Microbiome-based research is gaining credibility as a means to discover novel therapeutics. Now big pharmas like J&J and Pfizer are evaluating partnering opportunities in the burgeoning field – with potential therapies starting to enter the clinic – as they look to strike the appropriate balance between internal and external research.

The first therapeutics designed around manipulating the microbiome – the trillions of microbes living in and on the human body – are advancing through late preclinical development and approaching the clinic. The ability to mine the human microbiome to develop new drugs for a range of diseases from autoimmune diseases to metabolic disease to asthma is gaining credibility and big pharma wants in on the action.

Partnering in the field is poised to accelerate as big pharma dips its toe in, relying heavily on external collaboration to do so. Some big pharmas, notably **Johnson & Johnson**, are approaching the microbiome as a new area of research particularly aggressively, but several are looking to build expertise in the space.

"One of the things that has become apparent over the course of the last couple of years is that the microbiome has gone from an area that was provocative and interesting in the academic setting … [to] a space where there is increasing attention in the context of drug discovery and development," said Peter DiLaura, the CEO of **Second Genome Inc.**, one of several startups working in the field.

J&J Stakes Out Large Role In Microbiome

Among big pharmas, J&J is taking the most active approach to exploring the microbiome through its **Janssen R&D LLC**. The company stamped out its intentions in the field in February, with an announcement that it would establish theJanssen Human Microbiome Institute (JHMI) as a new research platform.

The company recruited a leading expert in the field, Dirk Gevers, previously of the **Broad Institute** of MIT and Harvard, to head the institute ("Janssen R&D Unveils Three New Research Platforms" — *"The Pink Sheet" DAILY*, Feb. 12, 2015). J&J has been the most active on the partnering front as well, announcing several research collaborations with academia and startups such as **Vedanta Biosciences**and Second Genome.

Janssen's Bold Vision For A Microbiome Institute

The new Janssen Human Microbiome Institute will focus on computational research, translational screening and clinical work, aligned with the J&J research unit's therapeutic area strategy, according to JHMI Global Head Dirk Gevers.

Others like **Pfizer Inc.** and **GlaxoSmithKline PLC** also confirmed they are investing in microbiome research, which likely could involve potential partners.

It is early days, however, and still unclear what might ultimately be the best approach to developing drugs that interact with the microbiome environment.

The belief is that the microbes living on the body and their interactions with the host play a fundamental role in human health, one that largely has been ignored; when the microbiome is unhealthy or skewed out of balance, it can lead to or contribute to disease. Much of the initial focus is on the gut microbiota, partly because its size – up to 100 trillion cells – exceeds the size of all the body's other microbial communities. And, the gut mediates a lot of other areas in the body.

The microbiome varies by person and is tractable, meaning that it changes based on outside factors like diet, infection or antibiotic treatment. Thus one of the biggest challenges at the moment is determining what exactly a healthy microbiome looks like.

"It's fair to say that our knowledge is just beginning," said Martin Blaser, director of New York University's Human Microbiome Program, addressing industry during a panel session on the microbiome at the BIO CEO & Investor conference in February.

Trying To Uncover The Best Approach

Significant correlative data linking changes in the microbiome to disease, coming mainly from academia, have been published, but less is known about the cause and effect of those changes. The successful use of fecal microbiota transplant – in which fecal matter is taken from a healthy donor and given to critically ill Clostridium difficile patients to restore the good bacteria in their intestines –thus far has been the main proof of concept in the field.

"The fact that we currently have all these associations is fascinating. [The microbiome] seems to be impacting many different diseases, but now translating this toward a product … will be one of the key challenges," said J&J's Gevers. Part of Gevers' work at the Broad Institute involved characterizing the microbiome in health and disease, including in Crohn's disease, type 1 diabetes and colorectal cancer, in connection with NIH's Human Microbiome Project.

One approach being explored by pharmaceutical startups like **Seres Health Inc.** and Vedanta is to develop a cocktail of bacterial spores that are then introduced into the microbiome to restore balance. Seres Health's lead candidate is SER-109 for the treatment of C.diff. infection. Vedanta's lead program, VE-202, is in development for irritable bowel disease and the Boston-based biotech recently partnered the asset with Janssen in exchange for up to $241 million including milestones ("Deal Watch: Roche/Foundation Medicine Highlights Hyper Deal-Making During J.P. Morgan" — *"The Pink Sheet,"* Jan. 19, 2015).

Others like Second Genome are working further downstream, exploring the connection between the microbiome and host processes. Second Genome is focused on discovering targets to inhibit or activate on the host side that have been impacted by changes in the microbiome.

Synlogic Inc. is developing synthetically engineered bacteria as a vector to produce and deliver drugs to treat disease. This work is peripheral to research focused directly on the microbiome but will be informed by

developments in the field. The startup is funded with a $29.4 million Series A investment from Atlas Venture and New Enterprise Associates.

Moving Toward The Clinic

While in all cases the research is at the very early stages, the first potential therapies are beginning to enter the clinic.

In January, Second Genome announced it initiated a Phase I multiple-ascending dose clinical trial for SGM-1019, for the treatment of inflammatory bowel disease. The drug inhibits an undisclosed target that Second Genome discovered to be a key driver of inflammatory bowel disease when modulated by changes in the microbiome.

The company hopes to be in a position to begin Phase II testing in 2016, and thus far it is moving the drug forward independently. “We are looking to take that forward ourselves,” CEL DiLaura said. “It’s really dependent on the indication space. There are some indications where it is going to be much more appropriate for us to partner.”

Janssen’s Miguel Barbosa, PhD, head of immunology research and scientific partnership strategy, predicted VE-202 is about 18 months from reaching the clinic. “Even though it is a new collaboration we just announced, the team is pushing on that IND,” he said in an interview.

VE-202 is a cocktail of Clostridia subspecies believed to alter the composition of gut bacteria and encourage the proliferation of regulatory T-cells, thought to be important in the treatment of IBD.

Janssen also has a partnership with Second Genome, a deal signed in 2013 to apply the San Bruno, Calif., company’s microbiome discovery platform to characterize the role of bacterial populations in ulcerative colitis with the goal of advancing novel targets (["Second Genome Scores A Deal With Janssen, A First In The Field Of Microbiome Therapeutics" — *"The Pink Sheet" DAILY,* Jun. 5, 2013]).

The two partnerships and technologies are quite different. “They really touch on how we have approached strategically the different aspects of this emerging field,” explained Barbosa.

“In one case, with Second Genome, we consider them to have one of the leading platforms for profiling the microbiota,” he said. That will help Janssen understand the differences in the microbiome between a healthy state and a disease state and delve deeper into the cause/effect relationship to hopefully identify a novel mechanism to modulate.

“For Vedanta, our interest is really to test the concept: can a live biotherapeutic achieve the therapeutic effectiveness that you would need a pharmaceutical product to have,” he said.

“We continue to probe these different types of aspects across the microbiome field with each of the partnerships and projects we take on, probing very unique aspects of the field we would need to be successful and build a large pipeline,” Barbosa added.

Partnering Pace Accelerates

More partnering is expected. It’s one of the key reasons Janssen established the JHMI, to position itself as a leading partner in the field. Evaluating external research is one of the primary job responsibilities for Gevers, who has significant ties to academia through his previous work.

“The fact that Janssen is making this statement of an institute is bold. It will attract people because it is a young field, [and] the expertise is still being built,” Gevers said. “It attracted my personal vision,” he added.

Other big pharmas also are testing the microbiome space, though perhaps more cautiously. Pfizer Senior VP BioTherapeutics Jose Carlos Gutierrez-Ramos said his company has been exploring the microbiome as an area of research for about five years.

“The focus for us has been what are the drugs, what do they look like, what is their therapeutic modality? Is it bacteria, a probiotic, is it a colonizing bacteria, is it a non-colonizing bacteria, is it a small molecule that activates the bacteria, a small molecule that mimics something that produces the bacteria,” Gutierrez-Ramos said.

“So our efforts for the last five years have been following the great biology that happens outside in academia and small companies, but at the same time, trying to figure out what is the best therapeutic modality for us to pursue,” he said.

One area of therapeutic interest for Pfizer is immune dysregulation and the impact of changes in the microbiome on local autoimmune diseases like inflammatory bowel disease, Crohn’s disease and ulcerative colitis. Another area of interest is the relationship between the microbiome, the immune system and metabolic disease.

More Pfizer Deals On Horizon?

Pfizer signed an agreement with Second Genome last year to run a large observational study in the area of metabolic disease, with the aim of evaluating clinical factors and the microbiome in approximately 900 individuals with varying metabolic phenotypes to better understand the relationship between the microbiome, obesity and metabolic disorders.

The company’s microbiome research will be highly externalized, Gutierrez-Ramos said. Pfizer has recruited a small core group of researchers who have knowledge of the field who will conduct some internal work but largely will be responsible for evaluating academic research and potential biotech partners.

“We have done due diligence on at least a handful of companies,” Gutierrez-Ramos said. “In the end, we decided at the time not to move forward with them, not because they were bad or good, but we felt the field was not ready or the technology was not ready.”

But that could be about to change. Gutierrez-Ramos indicated Pfizer is currently in advanced partnering discussions with two microbiome companies.

GSK also confirmed that it is conducting microbiome-based research, and others too are said to be probing the field from a deal-making perspective.

“The fact that big pharma is starting to take it seriously is only a good thing,” said Vedanta’s David Steinberg, currently CEO and a partner at the investment firm Puretech, which financed the company. “We had interest from multiple companies for VE-202. I see more companies stepping up in the microbiome space and building internal research capabilities.”

Before microbiome-based drugs become a reality, safety as well as efficacy will have to be proven out. It is still unknown if tweaking the microbiome could result in unintended consequences. But drug makers working in the field say they are confident that safety can be managed similarly to how it is in other areas of drug development.

“When you enter a new field there are always concerns,” acknowledged Barbosa. But he, like others working in the area, pointed out that the microbiome has been reprogrammed time and again following other drug treatments, antibiotics for example, but the changes just haven’t been evaluated.

“It is a great moment to do this,” Barbosa said. “There is a great explosion in science that will undoubtedly result in a great explosion of therapies. The question is when that explosion occurs.”