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Microbiotica entering clinic with live bacterial therapeutics

By Nuala Moran, Staff Writer

Microbiotica Ltd. is poised to advance two of its microbiome-derived products into the clinic after securing regulatory approval and fresh finance.

The first live bacterial therapeutic, MB-097, will be tested in combination with Keytruda (pembrolizumab) in patients with advanced melanoma who have not responded to treatment with immune checkpoint inhibitors.

The second product, MB-310, is a once-daily oral therapy for treating the inflammatory bowel disease, ulcerative colitis.

Tim Sharpington, CEO, Microbiotica

Both products were discovered using Microbiotica's microbiome profiling platform technology, which enables the identification of bacteria associated with favorable outcomes in defined patient populations, or in the case of ulcerative colitis, of the microbiome profile of healthy donors.

Starting the first-in-human studies is a major milestone for the company, which has been working toward this goal since it was spun out of the Wellcome Trust Sanger Institute in 2016 to commercialize the Sanger's microbiome culture collection.

Both studies will be initiated in the coming weeks, said Tim Sharpington, CEO of Cambridge, U.K.-based Microbiotica. "We are delighted to have been given two regulatory approvals in quick succession," he said.

The cocktail of nine bacterial strains in MB-097 initially was identified by Microbiotica's scientific founder, Trevor Lawley, in an observational study of patients with melanoma who responded to checkpoint inhibitors.

Checkpoint inhibitors have "really revolutionized" the treatment of melanoma and other cancers, Sharpington noted. But while the patients who benefit have significant responses, still only a relatively small number do so.

"The challenge is to understand why that is, and what we found was a small group of bacteria were significantly raised in abundance in responding patients," Sharpington said. "If patients had these bacteria in their gut microbiome before they started treatment, they were much more likely to respond," he told *BioWorld*.

Sequence data from four similar studies conducted around the world threw up the same microbiome signature. "When we looked at all the studies together, we could predict with 91% accuracy which patients were likely to respond, or not, based on their baseline microbiome," said Sharpington.

Research to understand the mechanism of action of the nine bacteria strains is a work in progress, he said. "But what we're seeing, is two distinct mechanism classes emerging."

The first is the ability to "tone" the immune system. This happens mainly via the bacteria interacting with dendritic cells in the gut. That stimulates core pathways of the immune system to activate cytotoxic T lymphocytes and natural killer cells.

Second, the bacteria produce metabolites. "What we're starting to understand is that these metabolites act directly at the site of the tumor, so it's not just potentiating the immune system," Sharpington said.

In the phase Ib trial, patients will be treated for six months with a combination of MB-097 and Keytruda. Merck & Co. Inc. will be supplying the checkpoint inhibitor.

"In essence, each patient will be their own control, because we're looking to rechallenge these patients with immunotherapy, after they've had their microbiome altered by our product," said Sharpington.

Gut epithelial barrier

In the case of MB-310, the defined microbial consortium was identified in healthy donors and has been shown to induce disease remission for a year in ulcerative colitis patients, when the bacteria were administered in a single fecal microbial transplant. The trial was conducted by Microbiotica collaborators at the University of Adelaide, Australia.

The bacteria associated with the therapeutic effect in ulcerative colitis dampen the immune system, with preclinical studies indicating this promotes repair of the damaged gut epithelial barrier, regulates the balance of inflammatory and immune-modulatory cytokines and induces a regulatory T-cell response.

It has taken significant effort to go from identifying the respective

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Continued from previous page

signatures to manufacturing supplies for the clinical studies.

A key hurdle was overcome when Lawley developed a technique for culturing anaerobic bacteria from the gut microbiome. Each bacteria strain is cultivated separately and freeze dried before being combined with its counterparts in a single enteric coated capsule that protects the contents from being degraded by gastric acids in the stomach.

"We've got nine bacteria in our oncology product, eight in our ulcerative colitis product… To scale up that manufacturing process is a huge amount of work… 17 different drug substances being processed in parallel," Sharpington said. "What really took the time was identifying the ideal growth conditions for each of the bacteria and growing them in GMP conditions."

Safety apart, one endpoint of the trials will be to demonstrate that the bacteria engraft and thrive in the gut. "This is where we isolated them from in the first place; we know they live there naturally. But this is our first-in-human study, so it is one of the things we will be checking. We hope they expand and grow. That's the equivalent of pharmacokinetics with microbiome products," said Sharpington.

There are no specific EMA or FDA guidelines for testing orally administered live bacterial products. As a result, it has "taken some time and a lot of discussion with regulators" to get approval for the clinical trials.

"Animal models really aren't very useful; classical toxicology can't really be done with these kinds of therapeutics. We have to establish the safety in humans, the fact that these come from healthy humans and are commensals, and we have to show they're non-virulent," Sharpington said.

One thing that has to be screened for "particularly carefully" is the absence of any gene that could confer antimicrobial resistance.

The existing investors who put $67 million into a series B in March 2022 have all followed on in an extension to the round. That provides the means to complete the two clinical studies, but the amount was not disclosed.

"It's been a difficult climate for biotech and microbiome in particular, and many companies have been forced to narrow the focus in their pipelines," Sharpington said. "We've had really exciting data preclinically in both programs; we were keen to run both studies and our investors were supportive of that."