Interview with MaaT Pharma

The promise of the microbiome in addressing cancer

The human microbiome is defined as the collective genomes of all the microbes, including bacteria, fungi and viruses, that live inside and on the human body. Most of these microbes do not cause disease. In fact, the body depends on many of these agents to metabolise drugs, stimulate the renewal of cells in the lining of the intestines and support the immune system[1]. Yet an estimated 25% of the world's population is affected by dysbiosis or a reduction in microbial diversity. This is associated with a rising incidence of metabolic and gastrointestinal diseases as well as disorders of the immune system.

One of the more recent findings of the scientific community is that the microbiome may play a role in the treatment of cancer. Specifically, two recent studies have shown that the transfer of faecal material from patients with melanoma who had responded to immune checkpoint therapy to patients who were refractory to these drugs, improved the efficacy of the checkpoint inhibitors[2,3]. These two studies, and others, have set in motion research on microbiome-based products that might fill a gap in the treatment of patients with solid tumours whose cancers are currently beyond the reach of the current immunotherapies.

One of the companies in the field is MaaT Pharma SA of France which has two faecal microbiome-derived products in clinical development and one preclinical product. The lead product, MaaT013, is in Phase 3 in patients with graft-versus-host-disease (GvHD) who are refractory to steroids, the standard of care first-line treatment, and to ruxolitinip, a second-line treatment. MaaT013 is also being investigated in melanoma. The second clinical product, MaaT033, is being investigated for the treatment of complications after allogeneic haematopoietic stem cell transplantation in patients with blood cancers. The preclinical product, MaaT03X, is expected to be studied in patients with solid tumours.

In an interview, Hervé Affagard, the company's chief executive, said he considers the new microbiome therapies to become "a sixth pillar in oncology." The other five pillars are surgery, radiotherapy, chemotherapy, small molecules and the new immunotherapies. The microbiome therapies "can play a role in combination with all of these," the executive said. With reference to the MaaT Pharma portfolio, he said the prospective cancer drugs should be eligible as standalone or as combination products.

There are currently no approved microbiome-based products for any indication globally. But there are at least two products close to registration in the US for a non-oncology indication – the treatment of *Clostridioides difficile* infections[4].

Mr Affagard co-founded MaaT Pharma in 2014, together with the microbiome scientist Joel Doré, who is currently an advisor to the company. Dr Doré is research director at the French National Research Institute for Agriculture, Food and Environment. In 2011, he helped launch the International Human Microbiome Standards Project which coordinated the development of standard operating procedures for comparing data from the human microbiome. Mr Affagard befriended Dr Doré whilst working on a thesis for a business degree. He had previously worked in the steel industry and then in healthcare. He subsequently became a venture partner at Seventure Partners. In the interview, he said his desire to explore the microbiome was linked to cancer diagnoses for two close family members.

In the eight years since MaaT Pharma's founding, the company has raised €73 million in capital of which €37 million is venture capital and €36 million came from an initial public offering of its shares on the Euronext exchange in Paris. The company's portfolio illustrates the evolution of microbiome-based technologies over the past eight years with a move towards oral therapies. The lead product MaaT013 which is currently in a Phase 3 trial for GvHD, is an enema formulation consisting of samples of faeces from multiple healthy donors. The samples have been rigorously screened for impurities with the result that only a small proportion of the donations are pooled for the final product.

A pooled enema formulation of MaaT013 is also being used in a recently launched Phase 2a clinical trial in patients with melanoma. This trial will investigate the therapy in combination with ipilimumab (Yervoy) and nivolumab

Maat Pharma pipeline, effective 20 July 2022

Drug	Indication	Drug type	Development Phase
MaaT013 (pooled enema)	Acute graft-vs-host disease	Onco-haematology	Ongoing Phase 3
MaaT033 (pooled capsule)	Post allogeneic haematopoietic stem cell transplantation	Onco-haematology	Completion of Phase 1b
MaaT013 (pooled enema)	Improving ICI responses in metastatic melanoma	Immuno-oncology	Ongoing Phase 2a
MaaT03X (fermented capsule)	Undisclosed solid tumours	Immuno-oncology	Preclinical

Terms: ICI=immune checkpoint inhibitor; pooled=pooled faecal samples from multiple healthy donors
Source: MaaT Pharma SA

(Opdivo), which are standard first-line checkpoint inhibitor treatments for this disease.

The company's second clinical product MaaT033 is a capsule also consisting of pooled faecal samples. MaaT033 recently completed a Phase 1B study in patients with acute myeloid leukaemia or high-risk myelodysplastic syndrome who had received intensive chemotherapy. The results were positive and preparations are underway to move this therapy into Phase 2/3 to improve the survival rate for patients following an allogeneic hemaetopoietic stem cell transplantation for blood cancers.

The company's technology platform then takes a further leap forward with MaaT03X, a preclinical product which is being manufactured in a co-fermentation process. Here, native faecal samples can be replicated at an industrial scale. Using artificial intelligence, MaaT Pharma expects to be able to make products that are specific for a cancer indication. "For the second generation product [MaaT03X] you would not collect from the donor anymore, [Samples] will be coming from a bank and from that you could produce as much material as you need," Mr Affagard commented.

The trajectory of the portfolio is to first establish a patient's response to the native faecal product and to then gradually move on to products that are easier to manufacture at scale. "As a proof of concept we are using MaaT013 in metastatic melanoma. But commercially, the product that we will develop is MaaT03X," the executive said.

MaaT Pharma's recently launched melanoma trial is being positioned as a test of findings that have been published in the scientific literature over the past 18 months. Currently some 60% of patients receiving anti-programmed cell death protein 1 (PD-1) therapies, known as checkpoint inhibitor therapies, do not respond to the therapy. Only 40% do respond. However separate studies published in the journal *Science* suggest there may be a way forward. In the first study, Diwakar Davar from the University of Pittsburgh, US, and colleagues investigated whether changes in the gut microbiota, or the microorganisms that live in the body, could help patients overcome resistance to anti-PD-1 therapy. In the study, a small group of patients were given faecal transplants from checkpoint inhibitor responders together with a checkpoint inhibitor. The patients had PD-1 refractory melanoma. The treatment had a clinical benefit for six out of the 15 patients.

A second study, reported by Erez Baruch from the Sheba Medical Center in Israel and colleagues, showed that faecal transplants and a reinduction of a checkpoint inhibitor produced clinical responses in three patients, including two partial responses and one complete response. The study also showed favourable changes in the immune infiltration of the cancers in the patients.

The Phase 2a trial of MaaT013 was initiated in early April and is being sponsored by Assistance Publique – Hôpitaux de Paris, the largest hospital system in Europe. The concept of the trial is to show that a pooled standardised faecal transfer will shift melanoma patients' gut microbiota towards a composition close to that associated with a better response and therefore will increase the response to a combination of checkpoint inhibitors[5]. According to clinicaltrials.gov, the study is the first randomised trial of a faecal microbiome transfer in patients with unresectable or metastatic melanoma. It is expected to enrol 60 people and last 37 months. Participants will receive the faecal transplant in combination with two checkpoint inhibitors or the two checkpoint inhibitors plus a placebo.

MaaT Pharma's approaches for treating cancer

Restore in haemato-oncology

Therapies for the treatment of acute graft-versus-host disease and the prevention of side effects from haematopoietic stem cell transplantation are restorative. The goal is to restore healthy microbiome functions and correct the impact of interventions such as treatments with antibiotics and chemotherapy.

Restore and modulate in immuno-oncology

Therapies for the treatment of solid tumours aim to restore and modulate the microbiome in order to improve a patient's response to immune checkpoint inhibitors.

In the interview, Mr Affagard said that MaaT Pharma wants to show that with some manipulation of the microbiome it will be possible to raise the 40% patient response rate to checkpoint inhibitors to something higher. "It starts with the restoration of local immunity within the gut and then that is going to have an impact on the systemic immune system as well," he commented.

Regulatory considerations

Both MaaT013 and MaaT033 are live biotherapeutic products which means that they would be regulated under the US Food and Drug Administration's Center for Biologics Evaluation and Research. A company with a live biotherapeutic would need to submit a biologics licence application (BLA) to the FDA in order to be approved for marketing. To date, the FDA has not approved any microbiome-based biotherapeutic products[6].

But MaaT Pharma would like to be first.

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This article was prepared by the *MedNous* editor on the basis of an interview with MaaT Pharma and a literature search.