EVALUATION OF A NEW CO-CULTURED MICROBIOME ECOSYSTEM THERAPY CANDIDATE (MAAT03X) FOR CLINICAL TESTING AS ADJUVANT/NEOADJUVANT TO IMMUNE CHECKPOINT INHIBITORS IN SOLID TUMORS

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Background
Increasing evidence suggests that gut microbiome composition modulates tumor response to therapies, including immune checkpoint inhibitors (ICI). Clinical proofs of concept were obtained in pilot studies using ICI-responder-derived fecal matter transplants to modulate the gut microbiome of non-responding cancer patients and improve their response to ICI.1 2 These results support the development of microbiome therapies replicating the effects of ICI-responders gut microbiome as adjunctive therapies to ICIs. MaT Pharma, a clinical-stage biotech pioneer in the development of Microbiome Ecosystem Therapies™ (MET) in oncology, has developed a unique, ground-breaking, patented pooled co-culture process (MET-C). This technology allows to replicate and leverage, at large industrial scale, the diversity of native-based microbiome ecosystems while tuning the resulting product according to indication-specific compositions.

Methods
We used several in vitro methods including Caco-2/THP-1 leaky gut model, AhR activation, PBMC assay and mixed lymphocyte reaction (MLR) to assess the impact of a MET-C candidate (MaaT03X) on gut homeostasis and immune activation.

Results
The impact of MaaT03X on gut barrier integrity was first evaluated in a Caco-2/THP-1 leaky gut model. While MaaT03X conditioned medium did not affect an intact gut barrier, it restored the integrity of a THP-1-induced damaged gut barrier. This was associated with a reduction of inflammatory signals. Increasing evidence suggests that microbiota-derived aryl hydrocarbon receptor (AhR) ligands maintain gut barrier integrity and function. Here, we assessed the impact of MaaT03X conditioned medium on AhR activation using a colon adenocarcinoma HT29-Lucia™ AhR reporter cell line. We observed a strong and dose-dependent activation of AhR receptor upon MaaT03X conditioned medium treatment. We then performed a human PBMC assay to further evaluate the impact of MaaT03X on immune cell activation. We observed the secretion of immunostimulatory cytokines associated with myeloid cell activation in response to MaaT03X conditioned medium. Notably, anti-CD3 mediated T-cells activation was further increased in response to MaaT03X conditioned medium as evidenced by increased IFNγ release associated with increased Granzyme B and CD25. Finally, MLR was performed to determine the immunomodulatory potential of MaaT03X through the interaction between T-cells and monocytes-derived dendritic cells (moDC). Interestingly, MaaT03X conditioned medium improved moDC maturation as well as moDC-induced T-cell activation. MaaT03X conditioned medium further increased anti-PD-1 mediated T-cell activation, as evidenced by IFNγ release.

Conclusions
Altogether, these results highlight the potential of MaaT03X to restore gut barrier integrity and stimulate immune cell response to ICI therapy, with potential benefit for solid tumors treatment.

REFERENCES

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