Evaluation of a new co-cultured microbiome ecosystem therapy candidate (MaaT034) for clinical testing as adjuvant/neoadjuvant to immune checkpoint inhibitors in solid tumors

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Abstract #6687

INTRODUCTION

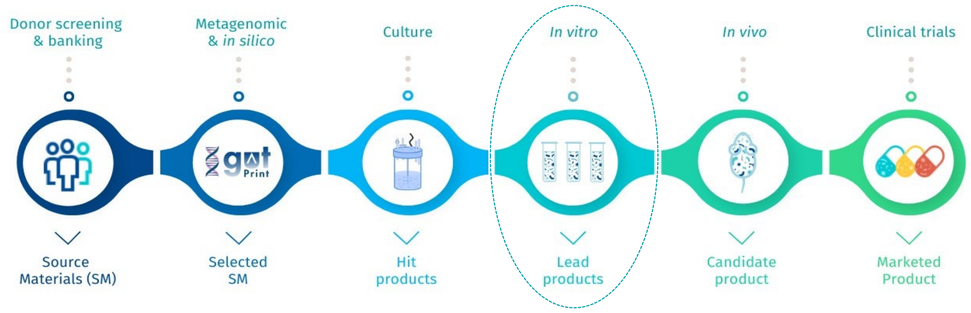
Increasing evidence suggests that **gut microbiome composition modulates tumor response to therapies**, including immune checkpoint inhibitors (ICI). Clinical proofs of concept were obtained using ICI-responder fecal microbiota transplants to modulate the gut microbiome of non-responding cancer patients and improve their response to ICI [1-4].

These results support the development of microbiotherapies replicating the effects of ICI-responders as adjunctive therapies. MaaT Pharma, a clinical-stage biotech pioneer in the development of **Microbiome Ecosystem Therapies (MET) in oncology,** has developed a unique, ground-breaking, patented co-culture process (MET-C).

This technology allows to replicate and leverage, at large industrial scale, the richness and diversity of native-based microbiome ecosystems while tuning the resulting product according to indication-specific compositions.

> The objective of this study is to assess the impact of a MET-C candidate (MaaT034) on gut homeostasis and immune activation.

METHODS

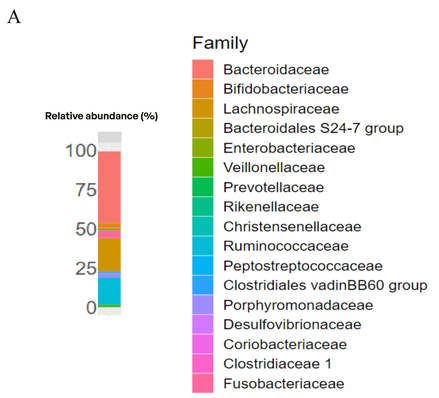


We assessed the impact of a MET-C hit product (MaaT034) on gut homeostasis and immune cell activation using a combination of methods:

- Metagenomic analysis
- Metabolite quantification
- Caco-2/THP-1 leaky gut model
- AhR activation
- PBMC assay
- Mixed Lymphocyte Reaction (MLR)

RESULTS

Metagenomic analysis reveals the richness and diversity of MaaT034 ecosystem



B

MaaT034			
Richness (OTU)	Inverse Simpson (OTU)	Core microbiota (%)	Butycore (%)
209	11	67	24

Figure 1. Metagenomic analysis of co-cultured MaaT034 ecosystem. 16S rDNA sequencing was performed to assess taxonomic classification and microbial diversity. **A)** Stacked bar plot of family relative abundances (top 95% abundant families). **B)** Richness (OTU), Inverse Simpson (OTU), % core microbiota and % Butycore® [5] of MaaT034.

MaaT034 produces key metabolites involved in gut homeostasis and response to immunotherapies

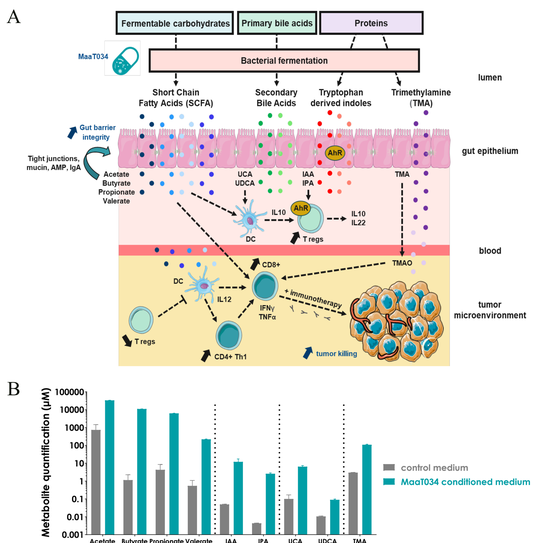


Figure 2. Metabolite quantification. A) Role of microbiota-derived metabolites in gut homeostasis and cancer response to immunotherapies [6]**. B)** The concentration of key metabolites released by MaaT034 in its conditioned medium was determined by LC-MRM/MS.

MaaT034 controls inflammation and restores gut barrier integrity in a Caco-2/THP-1 leaky gut model

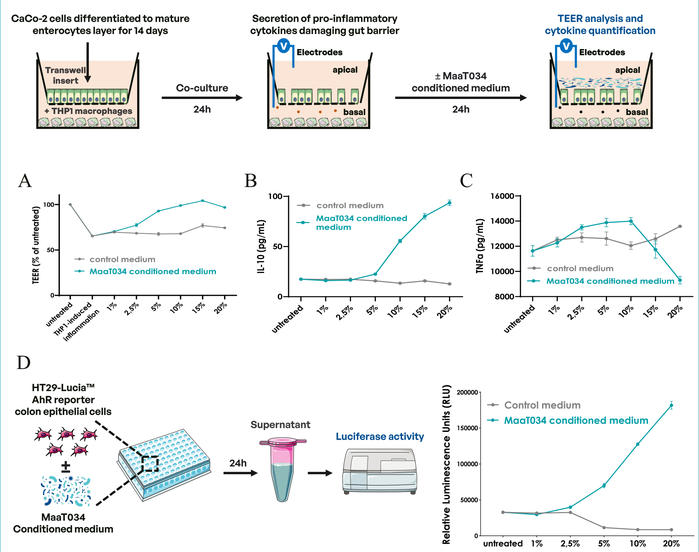


Figure 3. Impact of MaaT034 in a Caco-2/ THP-1 leaky gut model. **A)** Transepithelial electrical resistance (TEER) assay of gut barrier integrity. **B)** Anti-inflammatory IL-10 cytokine release. **C)** Pro-inflammatory TNFα cytokine release. **D)** AhR receptor activation in response to MaaT034 conditioned medium in HT29-Lucia™ AhR reporter cells.

MaaT034 promotes DC-mediated T cell activation

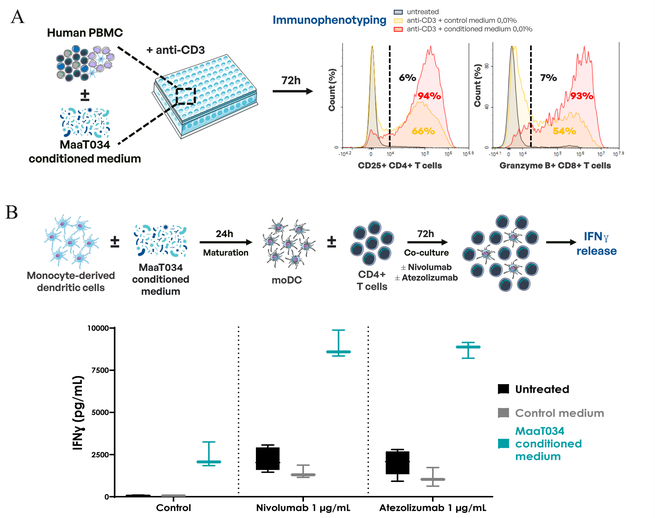
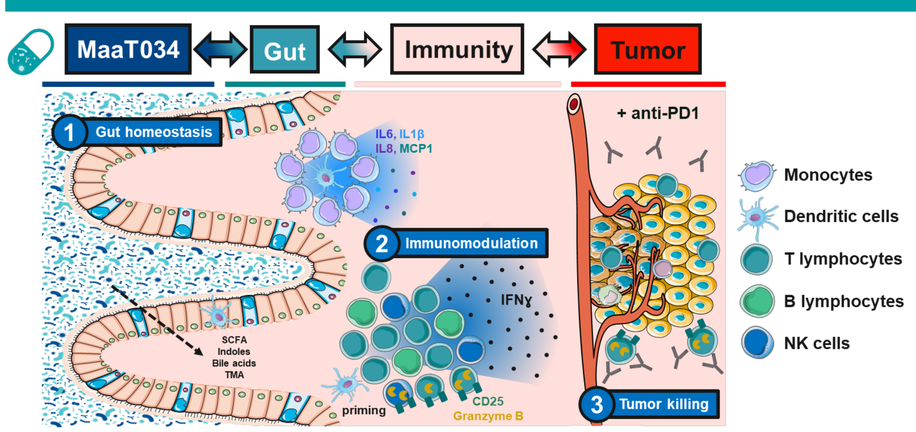


Figure 4. Impact of MaaT034 on immune cell activation. **A)** PBMC assay. Flow cytometry analysis of T-cell activation markers granzyme B and CD25 after PBMC treatment with 0,01% of MaaT034 conditioned medium in anti-CD3 activated conditions. **B)** Mixed Leukocyte Reaction (MLR) assay. Quantification of IFNγ release as a marker of T cell activation in response to 20% of MaaT034 conditioned medium or control medium in absence or presence of Nivolumab and Atezolizumab. Example of one out of two HLA-mismatched donor pairs.

CONCLUSIONS



MaaT034:

- **replicates, at large industrial scale, the richness and diversity** of healthy native-based microbiome ecosystems
- **produces key metabolites** associated with ICI response
- **restores the integrity** of a damaged gut barrier
- **activates AhR pathway** involved in gut homeostasis
- **stimulates both myeloid and lymphoid** immune cells
- **improves immune cell response to ICI therapy**

Altogether, these results highlight the potential of MaaT034 to restore gut barrier integrity and to stimulate immune cell response to ICI treatment.

> These outcomes paved the way for the identification of a promising frontrunner, MaaT034, slated for further advancements in clinical development.

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