MaaT034, a new co-cultured microbiome ecosystem therapy candidate, potentiates anti-PD1 mediated antitumoral activity in germ-free mice

Sheri Simmons[1], Julie Reygner[1], Charlotte Petitjean[1], Liyang Diao[1], Emmanuel Prestat[1], Aurore Duquenoy[1], Cyrielle Gasc[1], Sophie Declomesnil[1], Carole Schwintner[1], Kathy McCoy[2], Nathalie Corvaia[1], Bastien Laperrousaz[1]

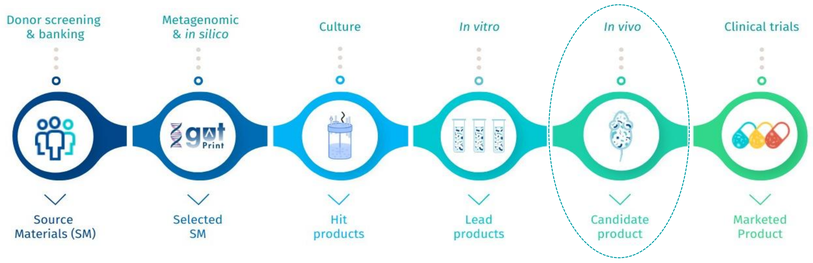
[1]MaaT Pharma, 70 avenue Tony Garnier, 69007 Lyon, France
[2]Department of Physiology and Pharmacology, Snyder Institute for Chronic Diseases, Cumming School of Medicine, University of Calgary, Canada.

Abstract #1150

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 is a late clinical-stage biotech leader in developing **Microbiome Ecosystem Therapies (MET) in oncology.** Its native, donor-derived, pooled MaaT013 product demonstrated positive pivotal Phase 3 results in acute Graft-versus-Host Disease and is currently being evaluated in a Phase 2a randomized multicenter exploratory clinical trial (IST) in metastatic melanoma. In parallel, MaaT Pharma has developed a unique, ground-breaking, patented co-culture process allowing to replicate and leverage, at large industrial scale, the functions of native-based microbiome ecosystems while tuning the resulting product according to indication-specific compositions. MaaT034, the first-in-class co-cultured microbiome product, is shown here to optimize intestinal homeostasis, activate key immune functions, and potentiate antitumoral activity in combination with an ICI treatment.

METHODS



We assessed the impact of MaaT034 on gut homeostasis and immune cell activation using a combination of methods:

- Metagenomic analysis (16S and shotgun)
- Germ-free mice
- Germ-free mice bearing MC38 tumors
- Metabolite quantification (LC-MS and GC-MS)
- Mixed Lymphocyte Reaction
- PBMC killing assay

The objective of this study is to assess the impact of the co-cultured MaaT034 candidate on gut homeostasis and immune activation.

RESULTS

MaaT034 reproduces MaaT013 microbial functions

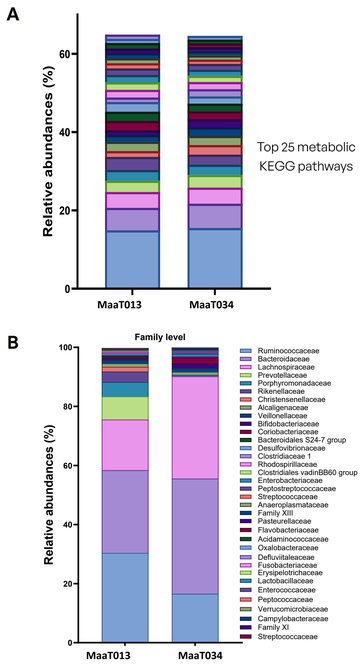


Figure 1. Metagenomic analysis of native MaaT013 and co-cultured MaaT034 ecosystem. A) The relative abundance of top 25 metabolic KEGG pathways as assessed with shotgun sequencing. **B)** Stacked bar plot of the relative abundance of bacterial families as assessed with 16S rDNA sequencing (excludes familles with RA <1%).

MaaT034 and MaaT013 potentiate anti-PD1 mediated activity in germ-free mice bearing MC38 tumors more effectively than *Akkermansia muciniphila*

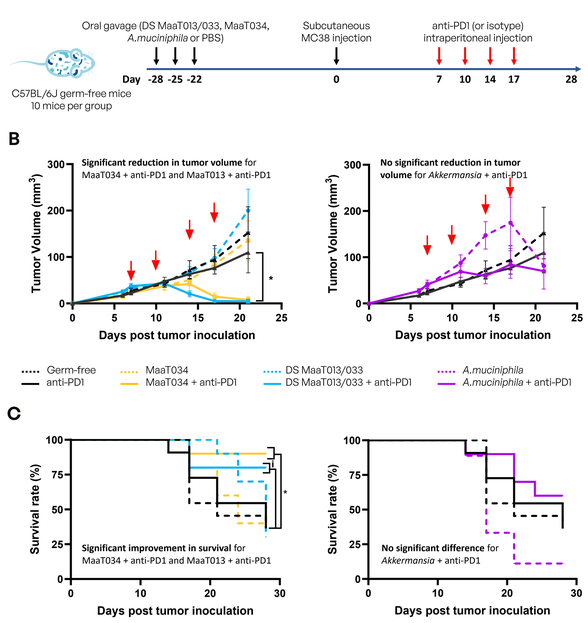


Figure 2. Anti-tumoral activity of MaaT013 and MaaT034 in combination with anti-PD1 in germ-free mice bearing MC38 tumors. A) Experimental design. **B)** Mean tumor volume (Left: MaaT013 and MaaT034; right: *Akkermansia muciniphila DSM 22959)*. **C)** Survival rate (Left: MaaT013 and MaaT034; right: *A. muciniphila DSM 22959)*. Results are expressed as mean ± SEM of 2 experiments (10 mice total). Chi-2 test for survival rate and mixed-effects analysis with Tukey's multiple comparisons test. * p<0.05, i p=0.06.

MaaT034 microbial species engraft in germ-free mice and produce key metabolites for gut homeostasis and immune modulation

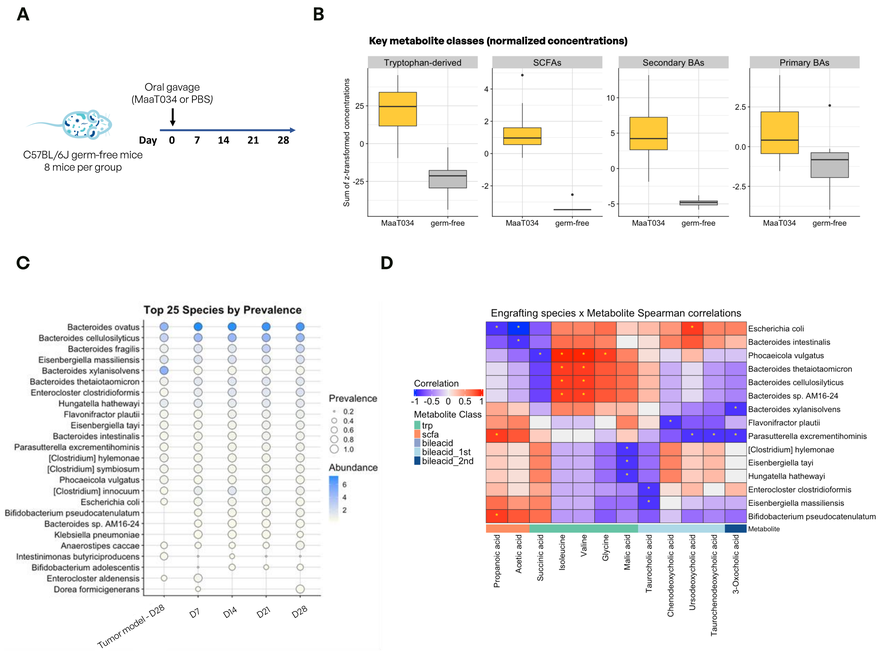


Figure 3. Impact of MaaT034 microbial species on production of key metabolites. A) Experimental design. **B)** Key fecal metabolites were quantified by LC-MS and GC-MS and are presented as the sum of z-transformed concentrations per class of metabolite. **C)** Shotgun rDNA sequencing of mice feces was performed to assess MaaT034 microbial engraftment in mice. Relative abundance and prevalence of top 25 microbial species are shown. **D)** Spearman correlation heat-map highlighting correlations between MaaT034-induced metabolites and engrafted microbial species. Stars indicate nominal p-value < 0.05.

MaaT034 promotes DC-mediated T cell activation and cancer cell killing *in vitro*

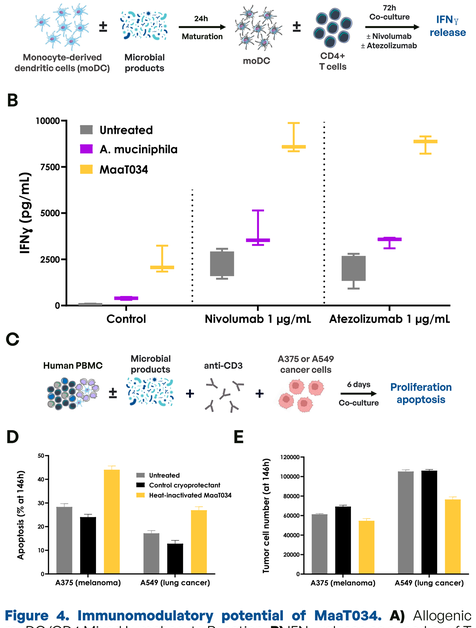
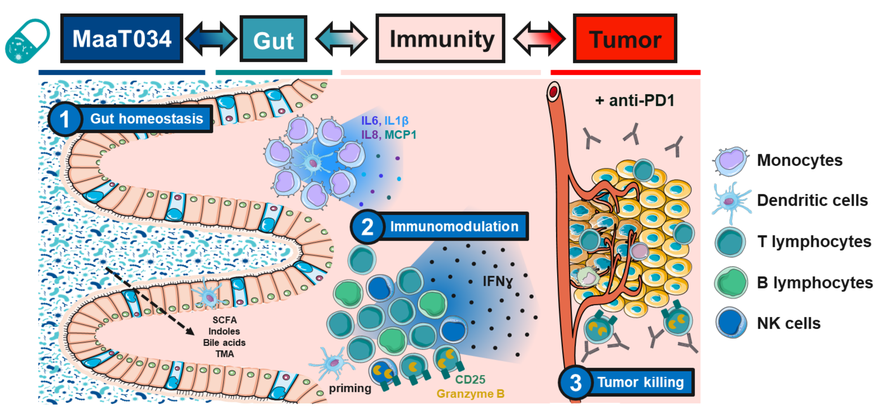


Figure 4. Immunomodulatory potential of MaaT034. A) Allogenic moDC/CD4 Mixed Lymphocyte Reaction. **B)** IFNγ release as a marker of T cell activation in response to MaaT034 or *A. muciniphila FAM66* conditioned medium ± Nivolumab or Atezolizumab. Example of one out of two HLA-mismatched donor pairs. **C)** PBMC killing assay. A375 melanoma and A549 lung cancer cell **D)** apoptosis and **E)** proliferation in response to anti-CD3 activated PBMCs ± heat-inactivated MaaT034 via IncuCyte S3™ live cell imaging.

CONCLUSIONS



MaaT034:

- **engrafts** durably in the gastrointestinal tract of germ-free mice
- **produces key microbial-derived metabolites,** replicating, at large industrial scale, the functions of healthy native-based microbiome ecosystems
- **Improves** gastrointestinal physiology
- **potentiates anti-tumor effects** mediated by anti-PD-1 checkpoint blockade in germ-free mice bearing MC38 tumors

Altogether, these results highlight the potential of MaaT034 to improve gut physiology and to potentiate **ICI mediated anti-tumoral response**.

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

REFERENCES

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