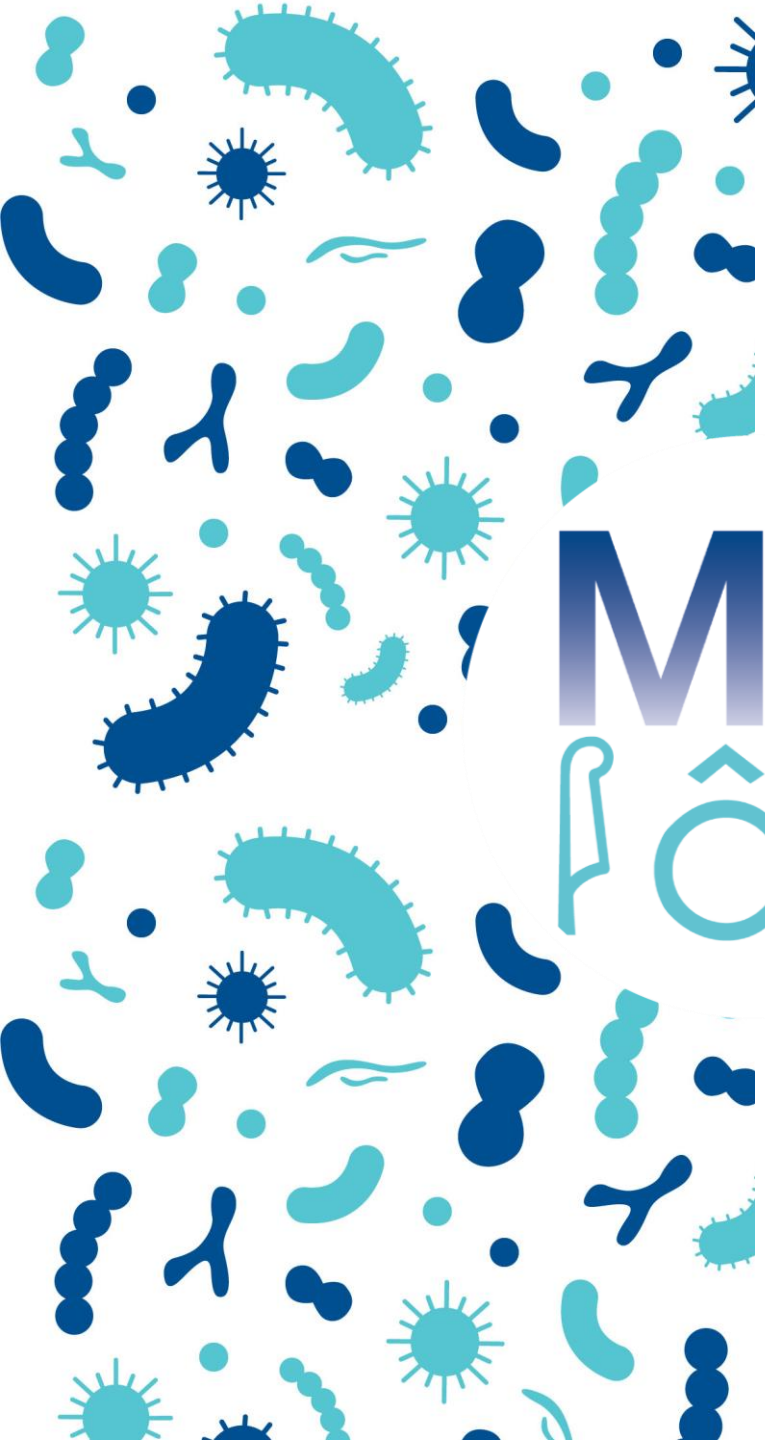
MaaT Pharma

Microbiota as a Therapy

SEPTEMBER 16th 2021

Approches innovantes en santé humaine, animale et environnementale dans la lutte contre l'antibiorésistance



MaaT Pharma's Microbiome Ecosystem Therapy Platform

MaaT Pharma's MET Platform has generated a diverse line of product candidates

gut Print

Data collection

Data analysis

cGMP Platform

Reproducibility

Gold standard

MaaT013

- ✓ High-richness/diversity
- ✓ Butycore™
- ✓ Pooled-donors

Completed Phase II

MaaT033

- ✓ High-richness/diversity
- ✓ Butycore™
- ✓ Pooled-donors

Currently in Phase I

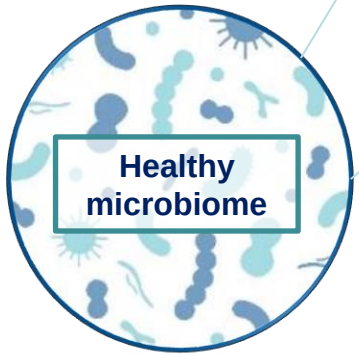
MaaT03X

- ✓ Full-ecosystem
- ✓ Tailored to specific indication
- ✓ Fermented

Preclinical

Both diversity and functionality matter

What is a healthy microbiome?



A diverse microbiome

Diversity = microbial community in terms of
- i) number of different microorganisms (richness)
- ii) their relative abundance, based on :
  - **Taxonomy** (identities of microorganisms)
  - **Function** (metabolic functions)

A balanced microbiome

Having a positive ratio of « beneficial / detrimental bacteria » to ensure a proper expression of the metabolic / immunological functions

⇒ **Beneficial bacteria**: anti-inflammatory and butyrate-producing bacteria *i.e* « Butycore »

⇒ **Detrimental bacteria**: pro-inflammatory bacteria *i.e.* Proteobacteria (that includes pathogenic bacteria such as Escherichia, Salmonella, Vibrio and Helicobacter)

Looking only at diversity will not allow to restore the full functionality of the microbiome.

Combination of diversity and balanced microbiome composition ensures the full therapeutic effect.

We ensure through GutPrint® that our drugs will fulfill all these characteristics

Our Integrated Drug Discovery Platform to Develop Microbiome Ecosystem Therapies

Patients (per indication)

Literature

Healthy donors

DATA OBTAINED FROM MULTIPLE SOURCES

Screening & drug candidate **assessment**

Biomarker **identification**

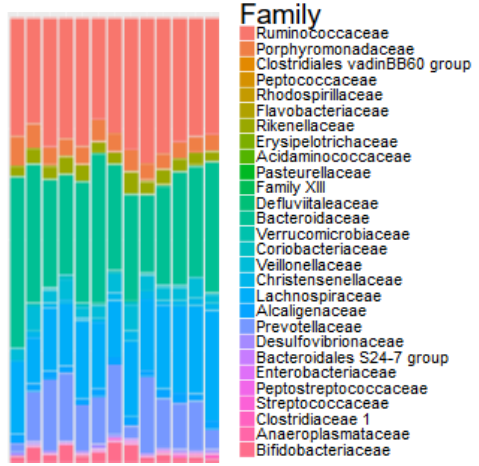
gut Print

Microbiome community selection

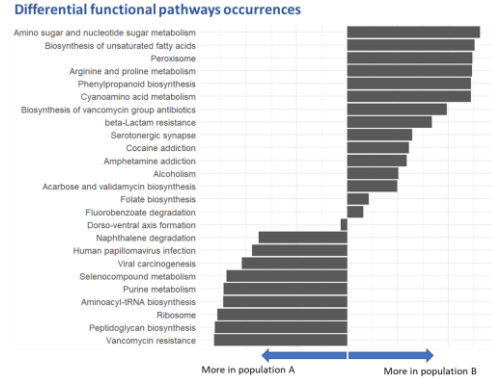
VALIDATION
(in vitro/in vivo)

MICROBIOME ECOSYSTEM THERAPY PRODUCT CANDIDATES

cGMP MANUFACTURING & CLINICAL TESTING



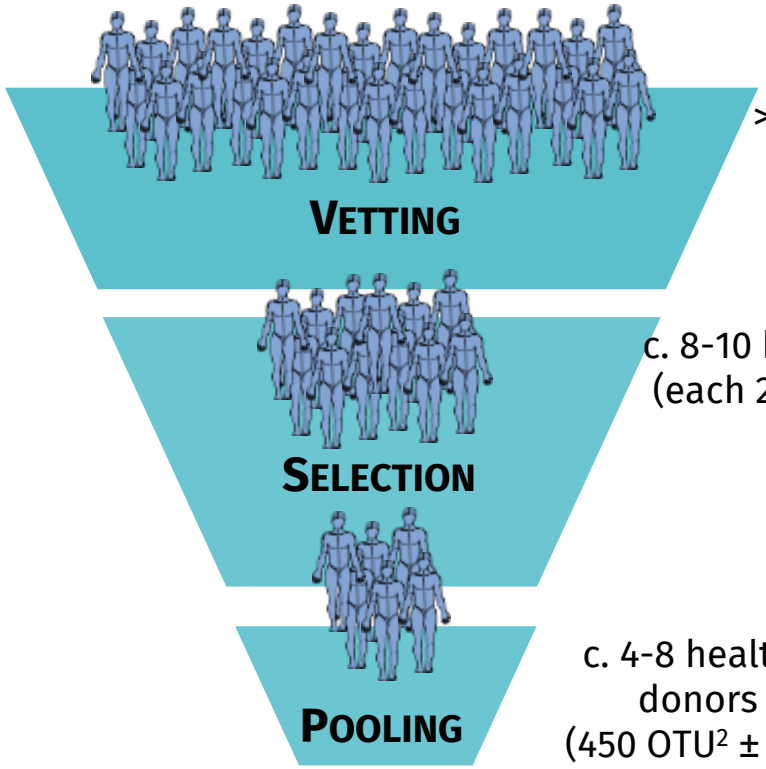
Supportive ecosystems



Functional analysis

MaaT Pharma's differentiated process creates product versatility with production adhering to the highest pharmaceutical standards (cGMP)

NATIVE cGMP PROCESS



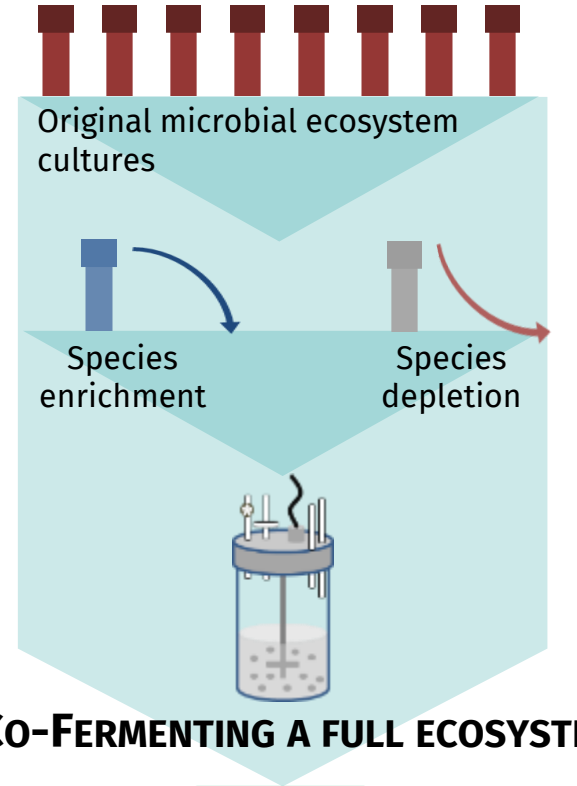
>3,000 candidates

c. 8-10 healthy donors
(each 274 OTU ± 15%)

c. 4-8 healthy donors
(450 OTU[2] ± 3%)

enema **MaaT013** MaaT033 capsule

FERMENTED cGMP PROCESS



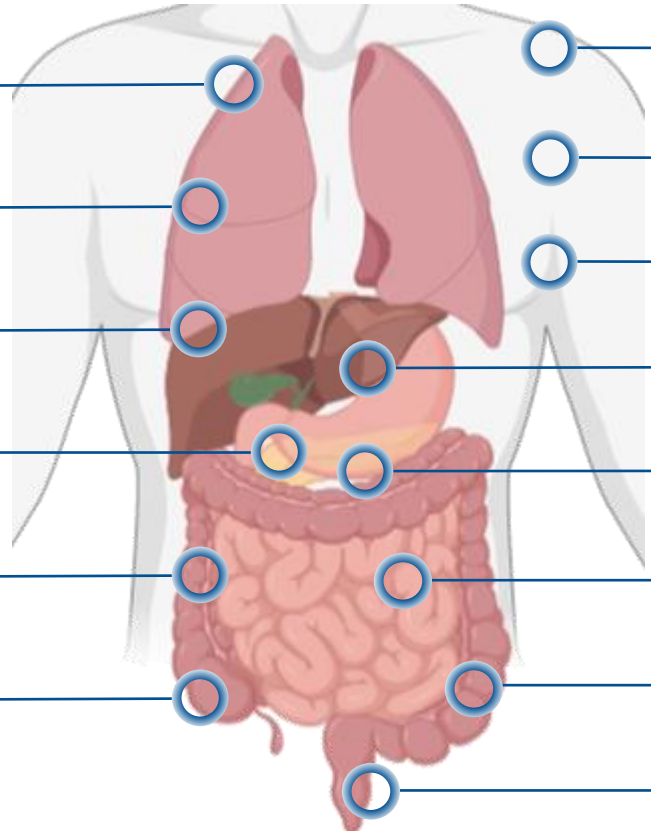
CO-FERMENTING A FULL ECOSYSTEM

capsule MaaT03X

- ✓ Standardized, off-the shelf, full ecosystem
- ✓ High, consistent richness and diversity
- ✓ Preserved Butycore[1]
- ✓ Designable
- ✓ High scalability
- ✓ Donor-independent

[1]15 different generas known to product short-chain fatty acids
[2]Operational taxonomic unit

The gut microbiome has broad potential implications in a variety of diseases



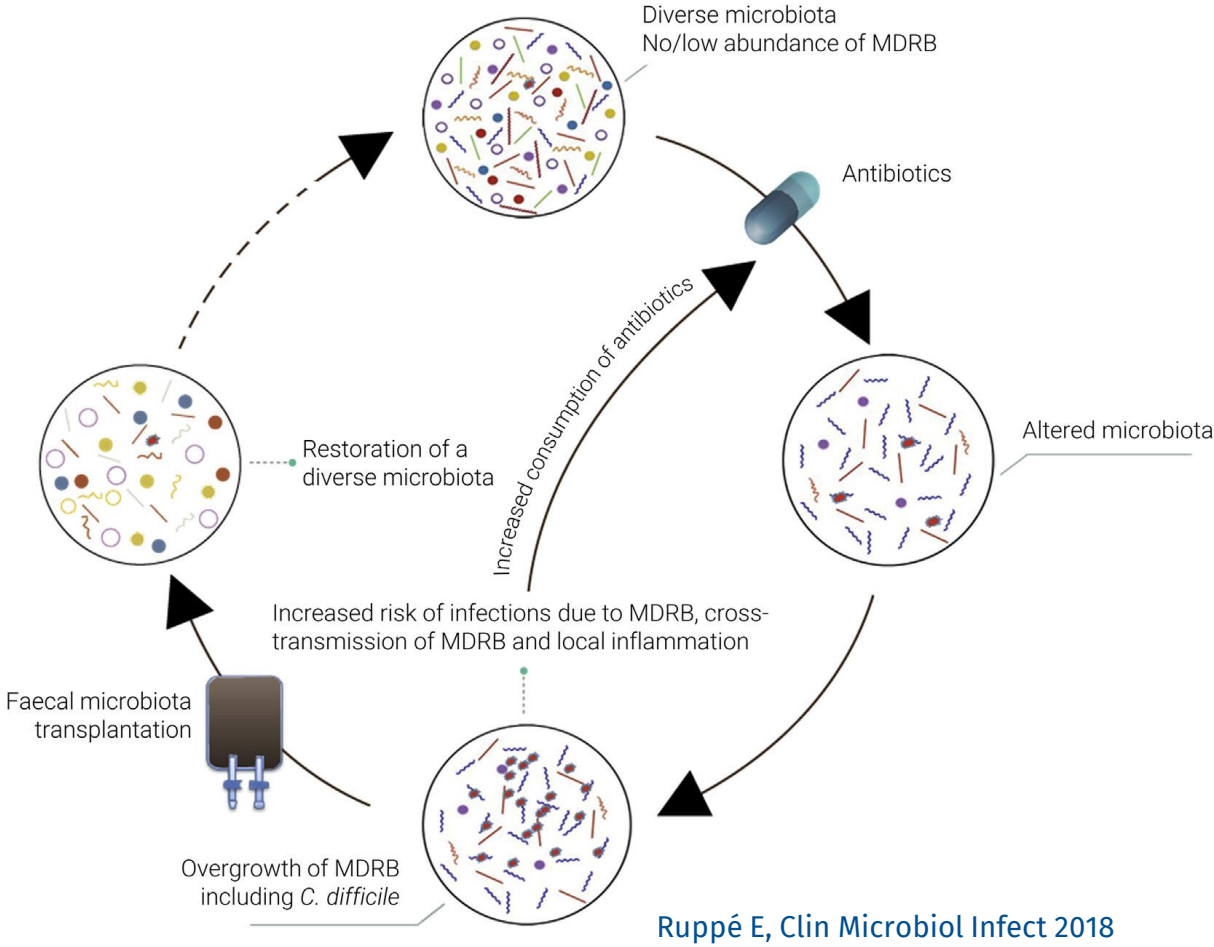
- Allergy
- Cystic fibrosis
- Liver pathologies
- Pancreatic cancer
- Ulcerative colitis
- C. difficile associated diarrhea
- HSCT for blood cancers
- Solid tumors
- GvHD post- HSCT
- Liver cancer
- Type 1, 2 Diabetes
- Obesity
- Chron's disease
- Colorectal cancer

[1]Abrahamsson, JACI 2012; [2]Han, Thorax 2012; [3]Rea, J Clin Microbiol 2012; [4]Le Chatelier, Nature 2013; [5]Qin, Nature 2014; [6]Qin, Nature 2010; [7]Gevers, Cell Host Microbe 2014; [8]Lepage, Gastroenterology 2011; [9]Kostic, Cell Host Microbes 2015; [10]Forslund, Nature 2015; [11]Tap, Gastroenrerology 2017; [12]Ma et al, Science 2018; [13]Gao et al, Eur J Clin Microbiol Infect Dis 2017; [14]Taur, Blood 2014; [15]Galloway-Pena, Cancer, 2016; [16]Wargo J L. Science 2018; [17]Zitvogel. Science 2018

MaaT Pharma is focusing on life-threatening diseases in oncology and hematology with high unmet need

The gut microbiome has broad potential implications in a variety of diseases

- Several case reports and retrospective cohorts describe FMTs performed in MDR bacteria-carrying patients
- Many clinical trials are ongoing (FMT/eradication/decolonization / antibiotic resistance > 20 studies in clinicaltrials.gov)
- Fecal microbiota transfer (FMT) could eradicate the digestive carriage of MDR bacteria via colonization resistance mechanism.

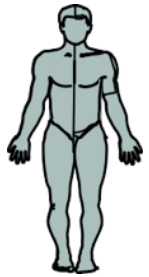


Ruppé E, Clin Microbiol Infect 2018

Acute Graft versus Host Disease (aGvHD) is an Unmet Medical Emergency

Treatment of patients with hematological malignancies often results in microbiome dysbiosis, leading to aGvHD

Hematological malignancy patients



Chemotherapy
Antibiotics
Irradiation
Immunosuppressants

Allogenic Hematopoietic Stem Cell Transplantation (allo-HSCT) c. 22,000 (c. 20,500 primary procedures and 7%-10% recurrent)[1] patients/year

Acute Graft-versus-Host Disease

Dysbiosis

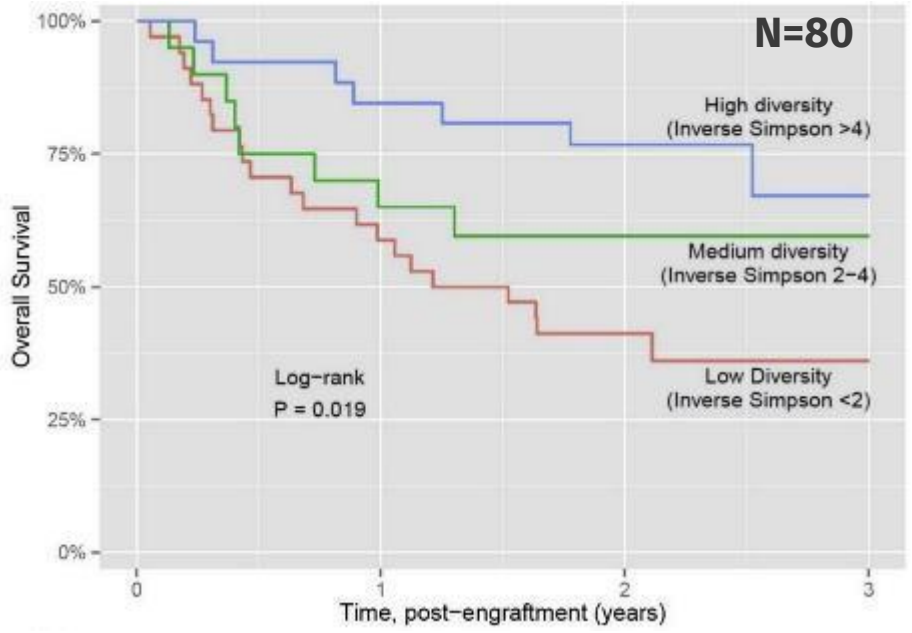
- Pathogen colonization
- Sepsis
- Neutropenic fever
- Multi-drug resistant bacteria

Approx. 10,000 patients/yr[1]
50% Steroid Resistant
70-90% 1-yr mortality
c. 60% with GI involvement

[1] EU5 + US + Japan

Gut Microbiota Diversity Drives Survival in Leukemia Patients Following Allogeneic-Hematopoietic Stem Cell Transplant

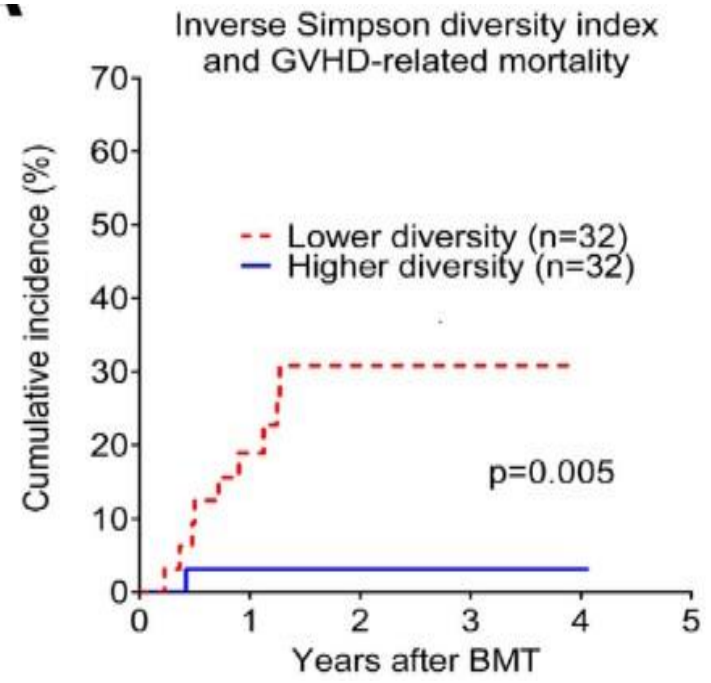
OVERALL SURVIVAL (OS) IN PEOPLE RECEIVING ALLO-HSCT



High diversity leads to 2x OS

Taur et al, Blood 2014; Taur et al, Best Pract Res Clin Haematol, 2014; Jenq et al, BBMT 2015; Holler et al, BBMT 2016; Simms-Waldrip et al, BBMT 2017; Weber et al, BBMT 2017; Malard et al, BBMT 2018

INCIDENCE OF GVHD IN PEOPLE RECEIVING ALLO-HSCT



-30% GvHD-related mortality

MaaT Pharma Microbiome Ecosystem Therapeutic Inverse Simpson (mean): **24**

The ODYSSEE Study: a POC study to demonstrate microbiome recovery in AML patients

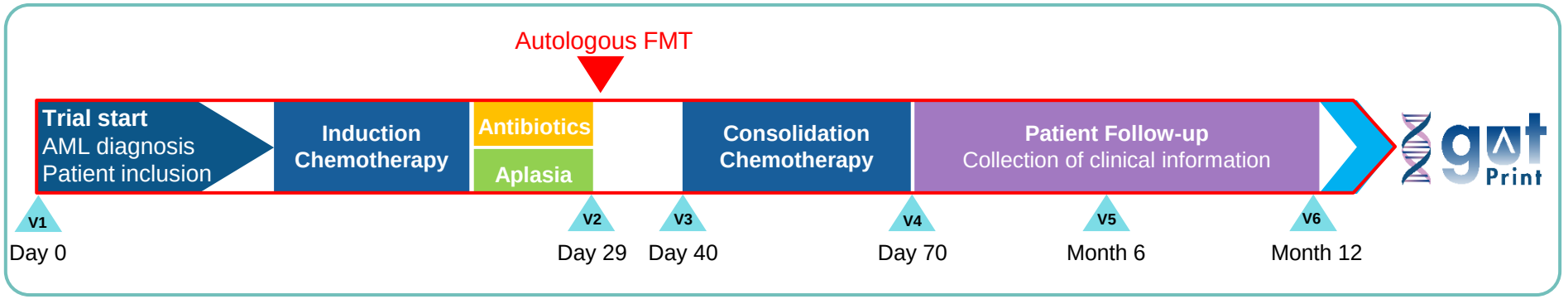
NCT02928523

OdysséE By MaaT Pharma

MaaT011 Autologous

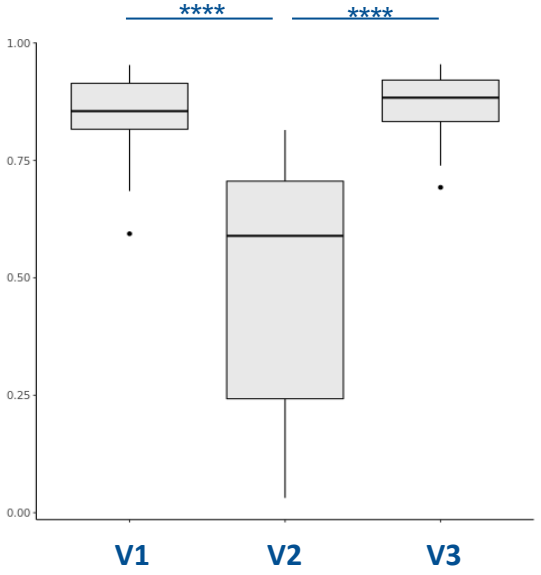
25 patients with **Acute Myeloid Leukemia** treated with MaaT011 (autologous FMT) with **12 months** follow up

7 sites in France



- **Primary objective: Impact of auto-FMT on recovery of microbiota diversity and correction of dysbiosis**
- Main secondary objectives:
  - ✓ Safety and feasibility of auto-FMT
  - ✓ Evaluation of auto-FMT on patient-related outcomes (clinical status, immune status and recovery)
  - ✓ Exploratory assessment of a dysbiosis biosignature

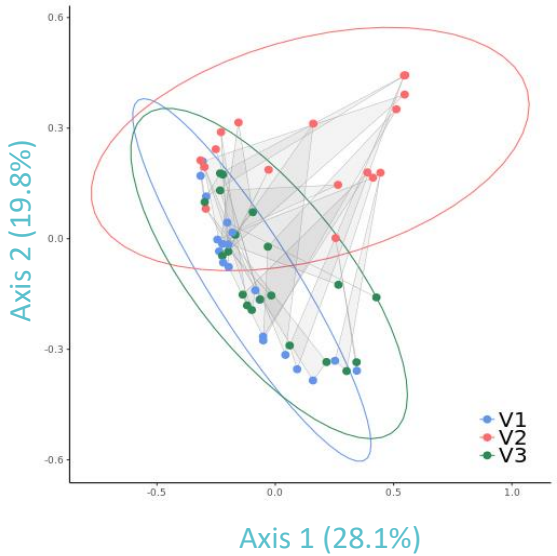
The ODYSSEE study: Demonstrated Microbiome Recovery in AML Patients



Simpson Index

Induction chemotherpay and antibiotics induce significant diversity decrease

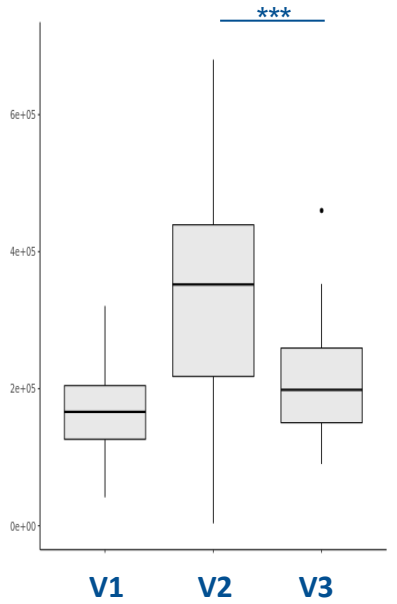
Auto-FMT restores >90% of baseline diversity



PCoA of Bray-Curtis Indexes

Dramatic microbiome structure shift after Induction Chemotherapy (V2)

Auto-FMT restores baseline taxonomic composition (V3 co-localized with V1)



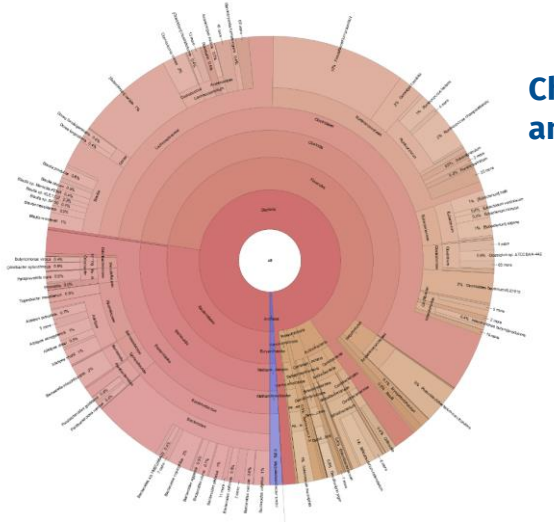
ABR copycount

43% reduction of antibiotic resistance gene copycount between V2 and V3

OdysséE By MaaT Pharma

The ODYSSEE study: Demonstrated Microbiome Recovery in AML Patients

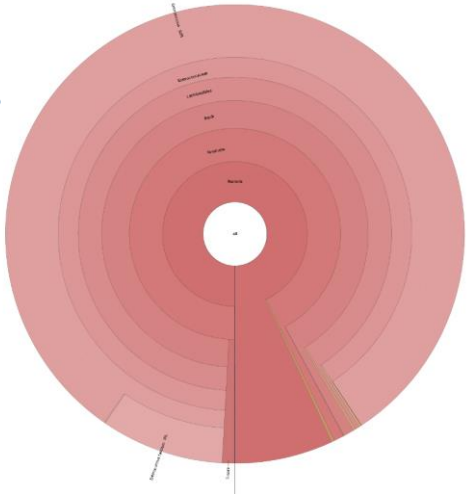
V1: AML diagnosis



Simpson Index: 0.91

Chemo / antibiotics

V2 (D29): impact of IC + ATB on microbiota, before FMT administration

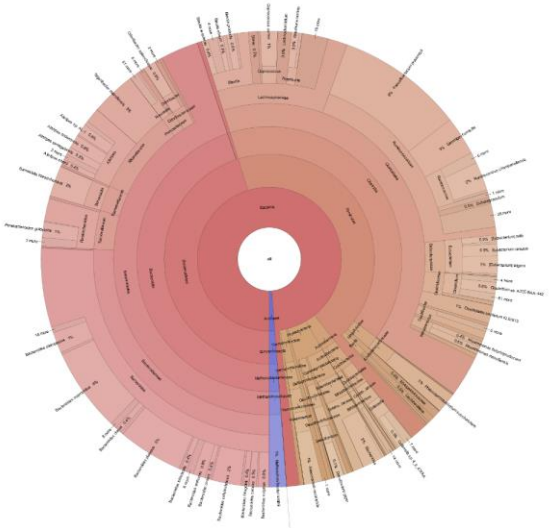


Simpson Index: 0.05

Enterococcus domination (90%)

MaaT011

V3 (D40): Evaluation of microbiota restoration, 10 days after dosing

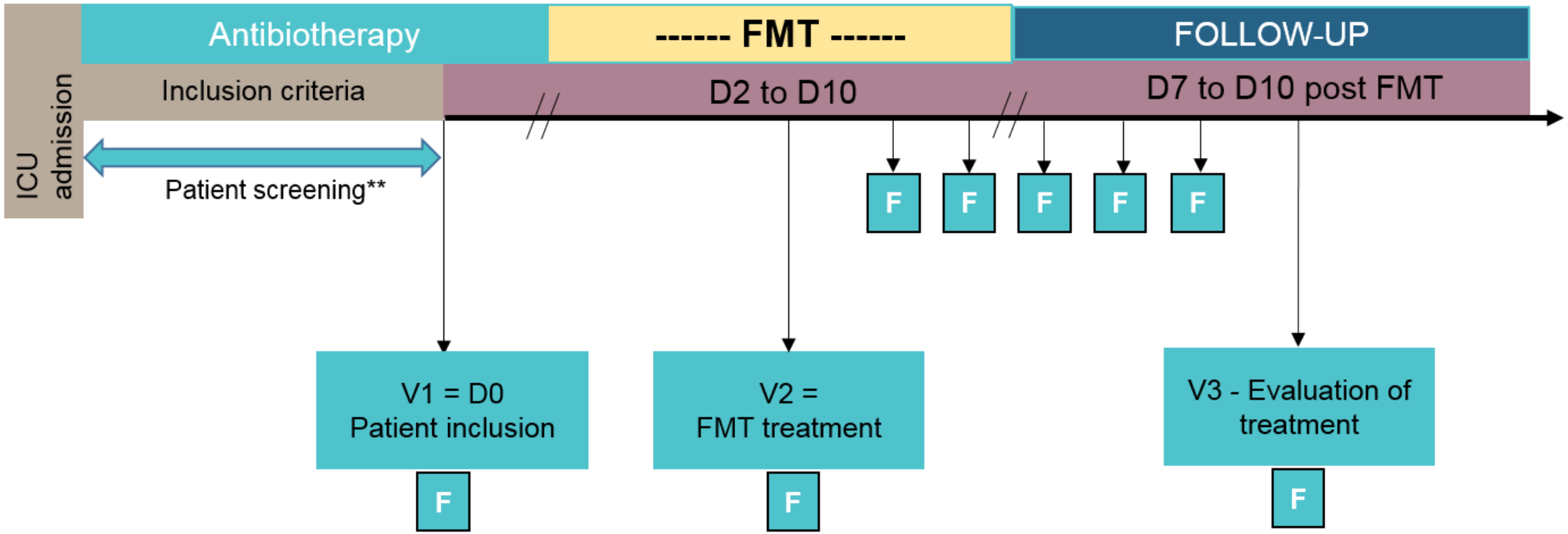


Simpson Index: 0.95

Bray-Curtis similarity V1/V3:
Species level 70%
Genus level: 80%

OdysséE By MaaT Pharma

The HAPY Study: “Evaluation of Heterologous fecal microbiota transfer in ICU Patients: A Feasibility and Safety Study”



F Fecal swab Collection: V1, V2, daily between 2 and 6 days after V2, V3

** Screening of the patient start after study information and signed consent form

The HAPY Study: a POC study to demonstrate safety, feasibility and microbiome recovery in ICU patients

Single-arm prospective exploratory study (Lille, Paris)

- Inclusion criteria
- ICU patient under mechanical ventilation
- MDR bacteria digestive carriage (rectal swab)
- Expected antibiotic duration < 10 days

Exclusion criteria

- Intestinal ischemia, toxic megacolon or gastrointestinal perforation
- Gastro-intestinal bleeding, abdominal surgery <3 months
- History of chronic digestive disease or gastro-intestinal resection
- Neutropenia, thrombopenia
- Immunosuppressive therapy

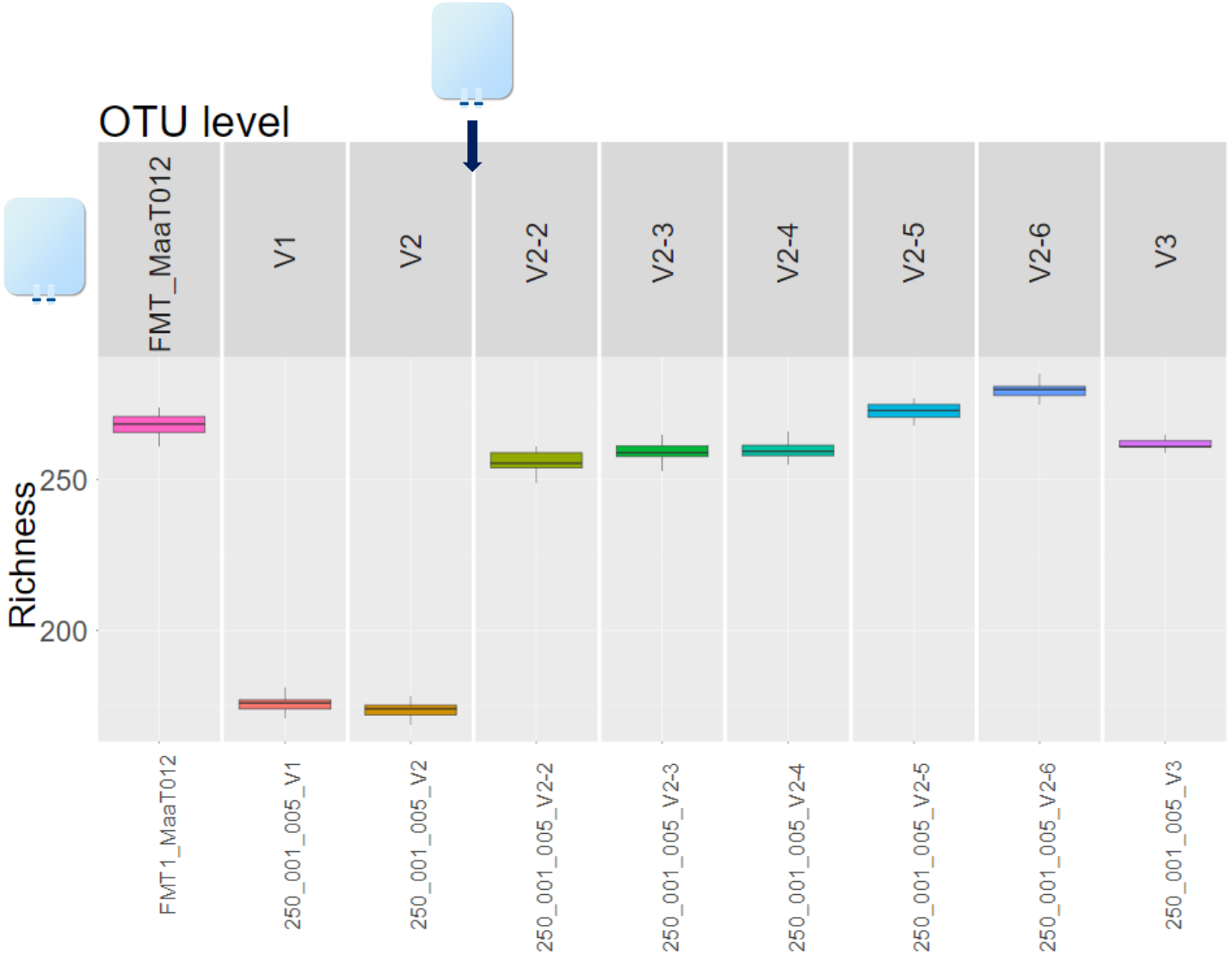
Intervention: frozen FMT (150 mL, 30g stool) by enema (Foley catheter)

6 patients treated
ESBL-E and/or CRE carriage
Mean SOFA 7
Mean Age 60

Safety of FMT: 5 SAE in 2 patients, non related to FMT (3bacteremia)
Feasibility of FMT Good, mean score 1,6/10
FMT Impact on MDRB carriage at D7-10 (culture)
Complete eradication: 0/6 patients
Partial eradication: 2/6 (ESBL-C. freundii, ESBL-K.pneumonia)

Metagenomic analysis

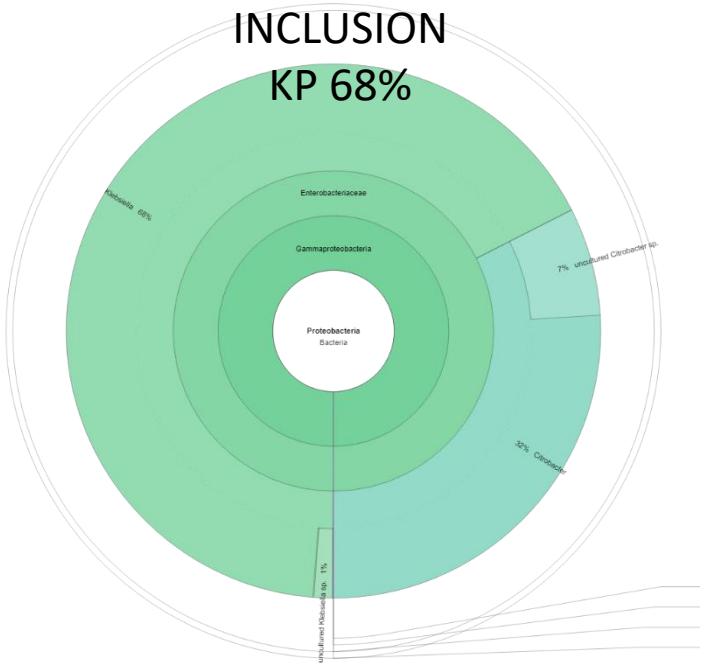
The HAPY Study: a POC study to demonstrate safety, feasibility and microbiome recovery in ICU patients



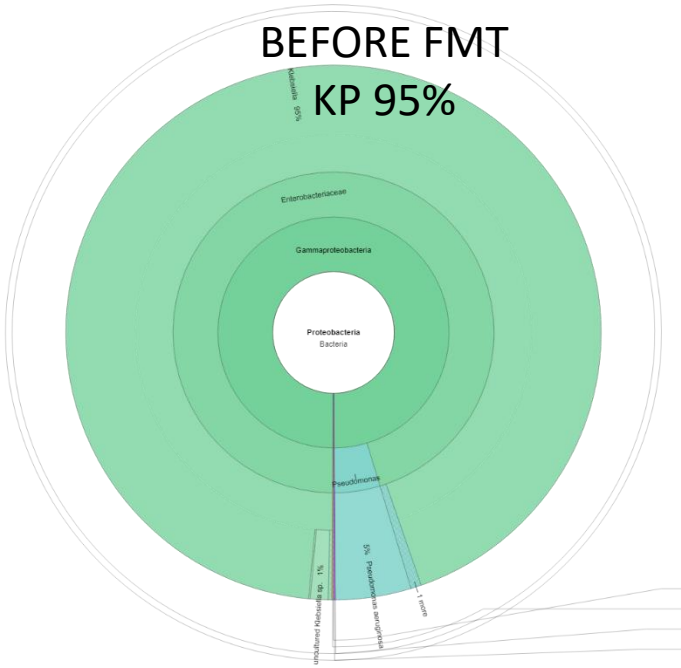
The HAPY Study: a POC study to demonstrate safety, feasibility and microbiome recovery in ICU patients

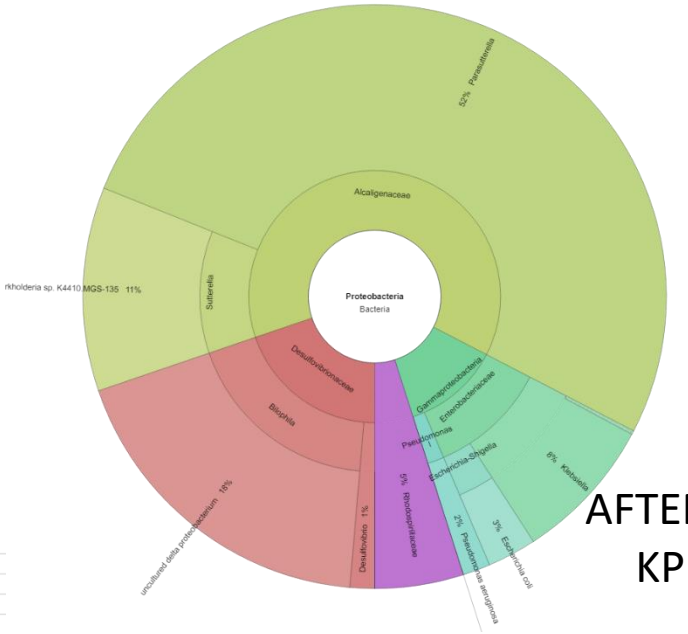
Visit	V1	V2	V3
BMR	KLEBSIELLA PNEUMONIAE (KP)	KLEBSIELLA PNEUMONIAE	KLEBSIELLA PNEUMONIAE
% of proteobacteria	68	95	8
Proteobacteria as % of bacteria	3	2	4

INCLUSION
KP 68%



BEFORE FMT
KP 95%





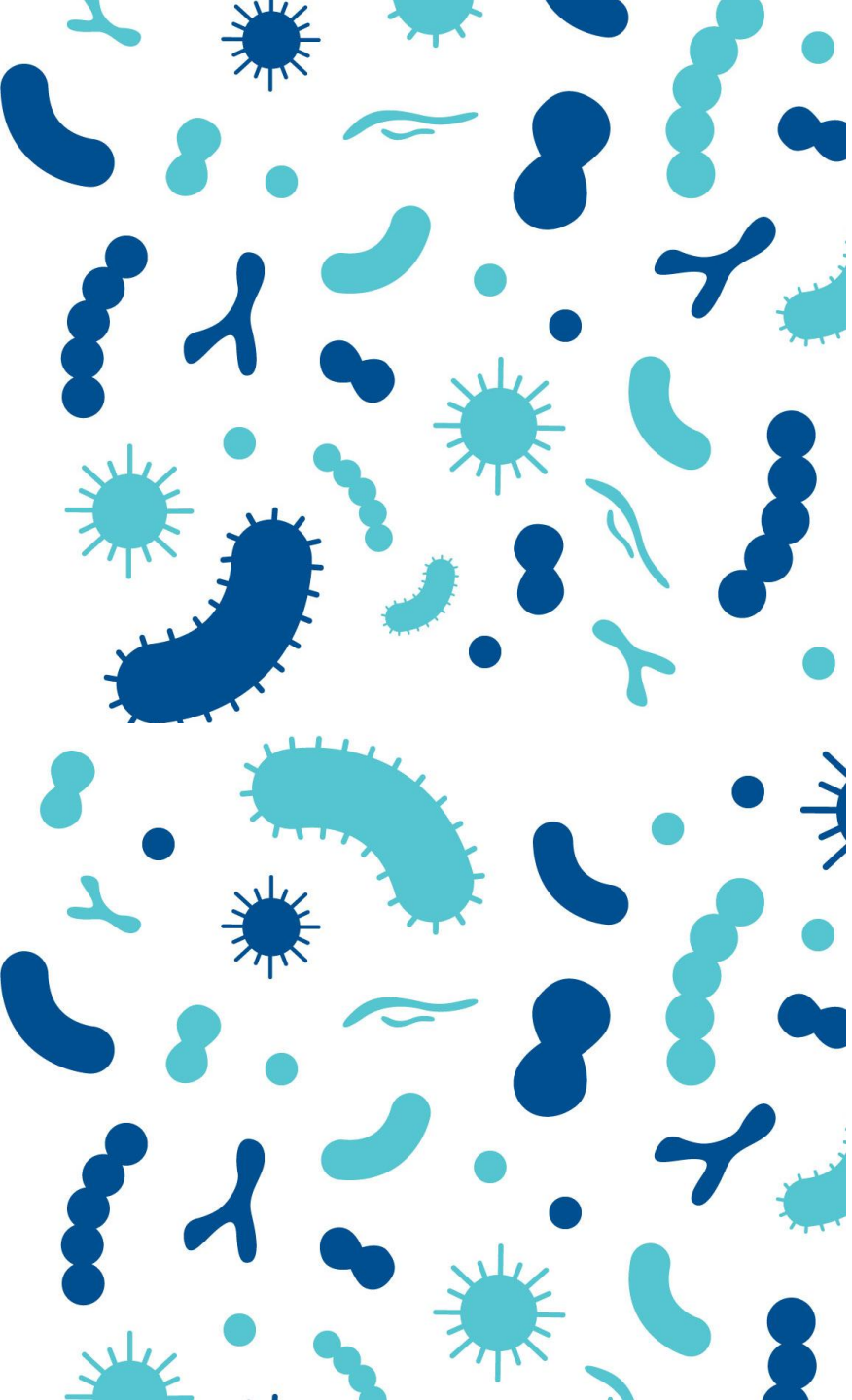
AFTER FMT
KP 8%

Conclusion: To be continued…

- Donors selection/vetting/safety
- Patients/donor match?
- Patients safety
- Resistome from sequencing data in complement to cultures
- Route of administration, dose regimen?
- Target? Which MDRB are resistant/sensitive to ecological exclusion?

How Contaminated Stool Stored in a Freezer Left a Fecal Transplant Patient Dead

Fecal bacterial colonies at a lab in Cambridge, Mass. Fecal microbiota transplants have proven effective in treating the deadly infection Clostridium difficile, but have not been approved by the F.D.A. Kayana Szymczak for The New York Times

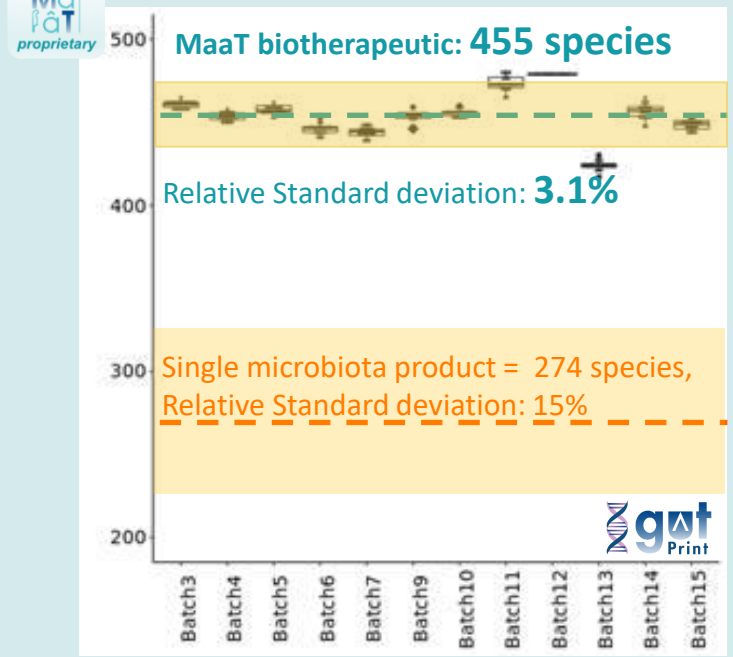


THANK YOU

Reproducible high microbial diversity biotherapeutics

A single active substance
characterized by high diversity and richness

Microbial richness



in two formulations

MaaT013

- Enema for direct colonic delivery
- 80% restoration
- 1 bag > 10^{11} CFU
- 18 months stability

MaaT033

- Capsule for ileocolic delivery
- 1 capsule > 10^{10} CFU
- Ease of administration

Well-characterized, potent, highly stable biotherapeutics manufactured via **reproducible batch methods under cGMP conditions from pooled donors**