MBIO 2018

adebiotech

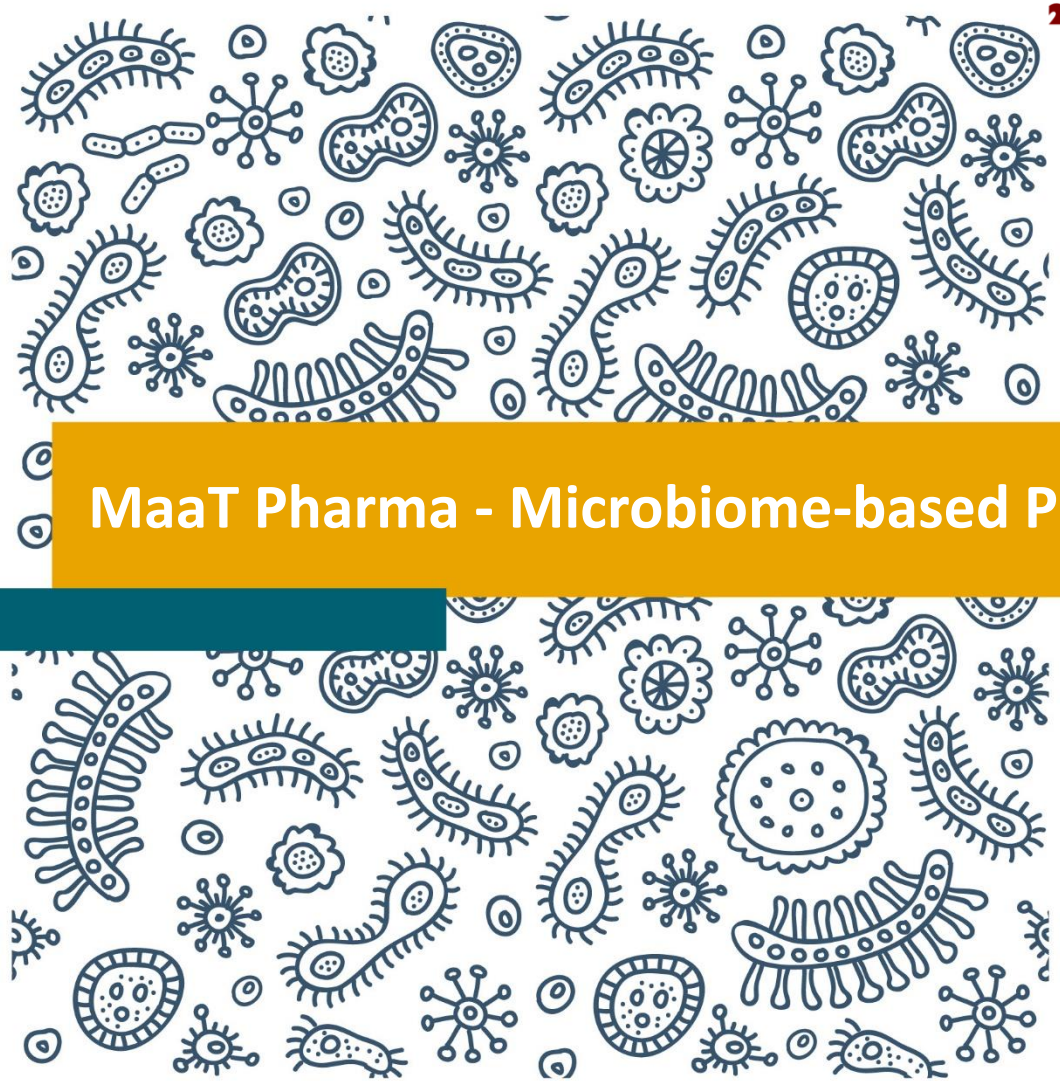
19 & 20 JUIN 2018

Les microbiotes

et la santé humaine, animale et environnementale :
Prévention et traitements du futur

Biocitech Romainville-Grand Paris

MaaT



MaaT Pharma - Microbiome-based Products CMC Development

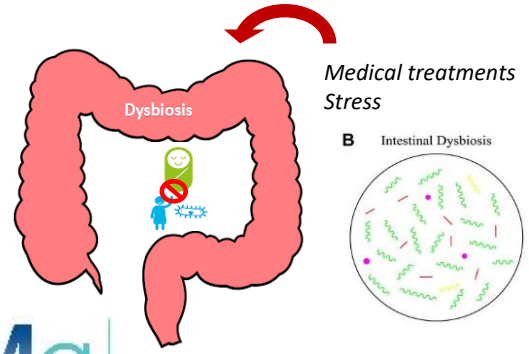
A FAST GROWING COMPANY LEADING FMT-BASED PRODUCT IN EUROPE

- ***Breakthrough technology:***
  Next generation Fecal Microbiota Transfer (FMT)
- ***Market entry strategy:***
  Oral and Enema FMT in hematology oncology
- ***Mission:***
  To restore the Man-Microbes symbiosis
- ***IP***
  5 Families of Proprietary and owned patents

- ***Status***
  Clinical, Phase 2 in GvHD initiated
- ***Next step:***
  Launch of a Phase II in Leukemia
- ***Funding:***
  12 m€ plus 4 m€ non dilutive
  Currently raising 16 m€
- ***Date of incorporation:***
  Dec. 2014
- ***FTE:*** 20+

RESTAURATION OF THE MAN-MICROBES SYMBIOSIS

➢ **The Microbiota can be described as** a highly diverse ecosystem of 100 trillion bacteria **living in symbiosis in the human gut** with more than 200 different bacterial species for each individual

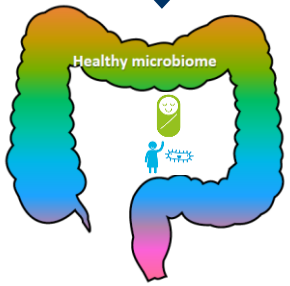


Medical treatments
Stress

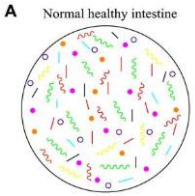
Dysbiosis

- **Leaky gut barrier**
- **Reduced diversity and loss of protective µorganisms**
- **Low-grade to overt inflammation**
- **Unbalanced oxidative stress**

MaîâT

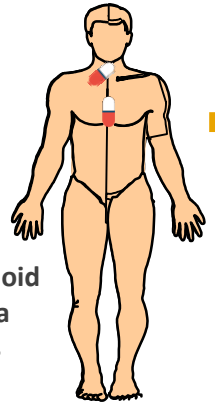


Symbiosis restoration



- **Strong gut barrier**
- **High diversity and protective µorganisms**
- **Balanced immune response**
- **Limited oxidative stress**

HEMATOLOGY-ONCOLOGY DRAMATICALLY IMPACT PATIENTS' MICROBIOME



Acute Myeloid Leukemia Patients

AML treatments

Cycles of intensive chemotherapy

Massive antibiotherapies during aplasia

HSCT conditioning regimens

Total Body Irradiation

Chemotherapy agents

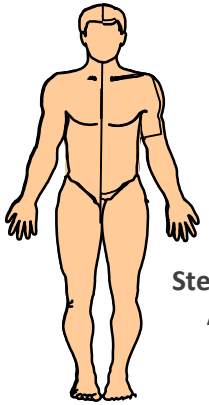
Allo HSCT

Acute GvHD

Immunosuppressive drugs

First-line acute GVHD treatment

Corticosteroids



Steroid refractory Acute GvHD Patients

MaaT033

Prevention of microbiota alterations and complications

Iatrogenic microbiota alterations

MaaT013

Restoration of microbiota and aGvHD treatment

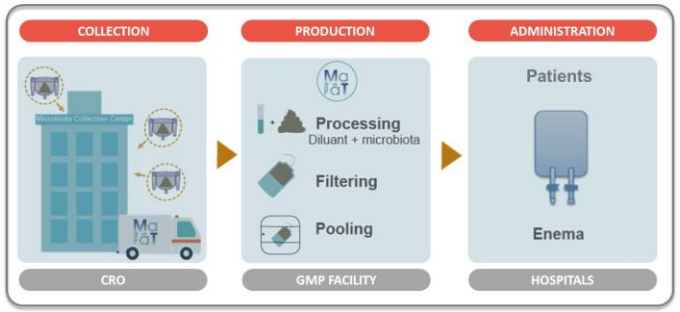
Sepsis, Infections with multi-drug resistant bacteria, Organs failure, acute GvHD …

MAAT PHARMA'S PLATFORMS

RESEARCH

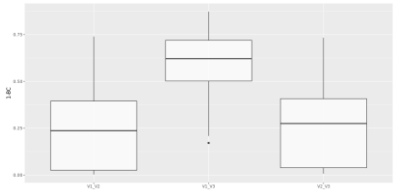
- Tailored microbiota based on medical needs
- Microbiota delivery
- Microbiota processing
- *in vivo* / *in vitro* preclinical dysbiosis assessment
- Analytical assays

PHARMACEUTICAL DEVELOPMENT



CLINICAL DEVELOPMENT

OdysséE By MaaT Pharma



HERACLES By MaaT Pharma

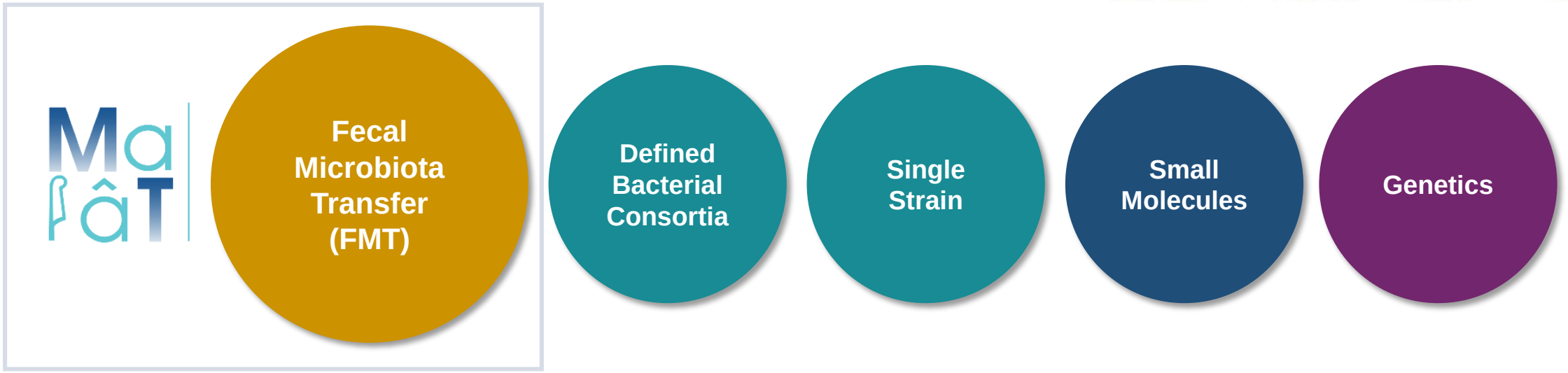
BIG DATA SYSTEMIC ANALYSIS PLATFORM

- Symbiosis characterization for donors *(30+ donors)*
- Dysbiosis characterization for patients *(100+ patients)*
- Actives identification based on clinical screening and compassionate use *(in progress)*
- Biomarkers *(in progress)*

gut Print

- OMICS, including Strain analysis (1,000+ analysis)
- Qualified Batch Released (30 lots – 500 units)
- Culture medium selection for tailored microbiota culture
- Preclinical and stability studies based on taxonomy (5 projects)

BREAKTHROUGH TECHNOLOGY : FMT AS NEW CLASS OF THERAPEUTICS



FMT

- **Used in the US** sporadically since the 50's as compassionate use
- **Recognized by FDA** as an investigational drug since 2013, and in the majority of **European countries.**
- **Validated as a therapeutic option** for *Clostridium difficile* infection : 90% efficacy (3x greater than the standard of care)
- **Being assessed as a therapeutic option** in other indications (**Hemato-Oncology**, GvHD Metabolic disorders, IBD, Crohn's Disease, etc…)

FMT STATUS AND FUTURE

- **FMT is primarily used for compassionate use in hospitals**
- **Manufacture within the hospital.**
- **No approved drug or alternative supply exists.**

Arroniadis O. et al. , The New Gastroenterologist, 2016

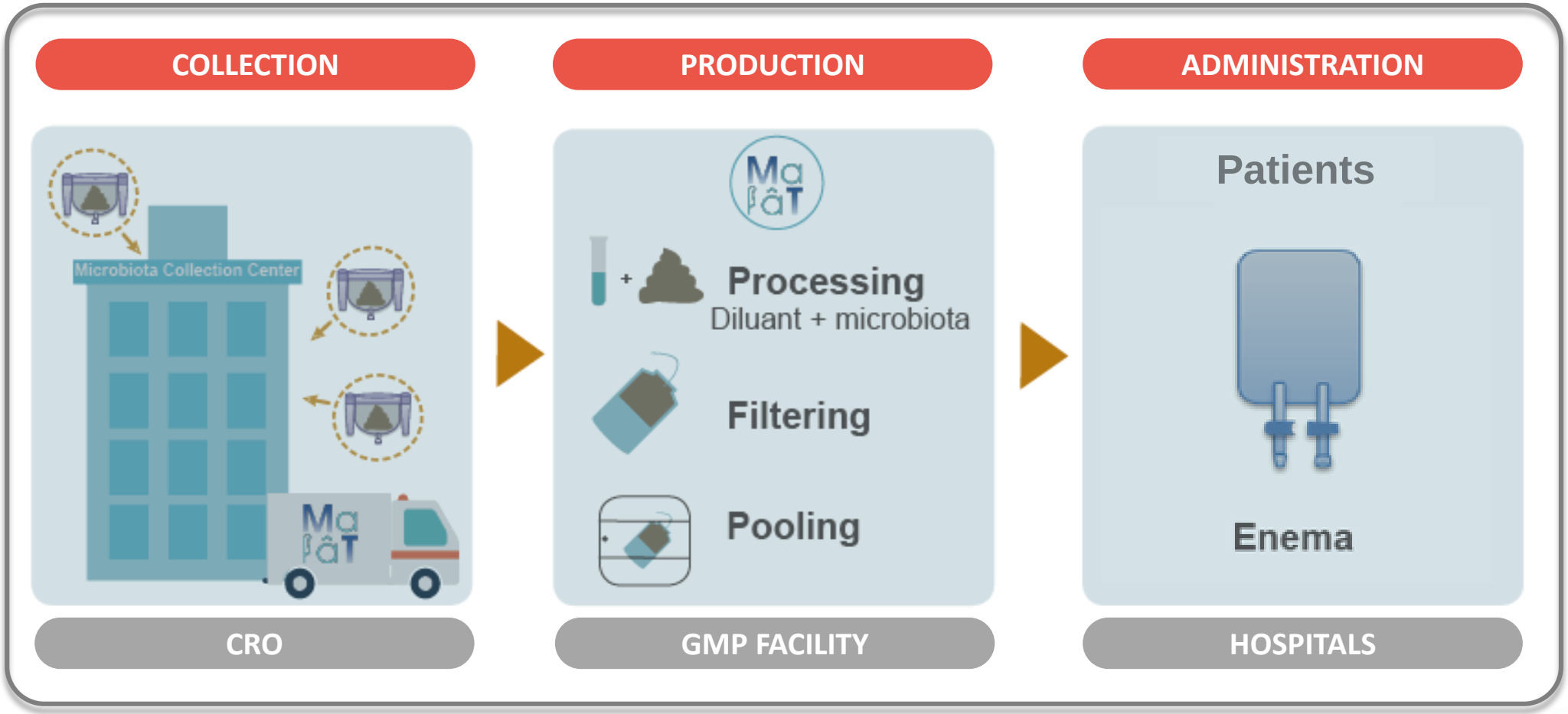
- **Tremendous work and research from Physicians in order to define standards of clinical practice**
  (Creation of National, European and International groups)
- **Development of new guidances with the regulatory agencies**

Cammarota G, et al.
*Gut 2017;**66**:569–580*

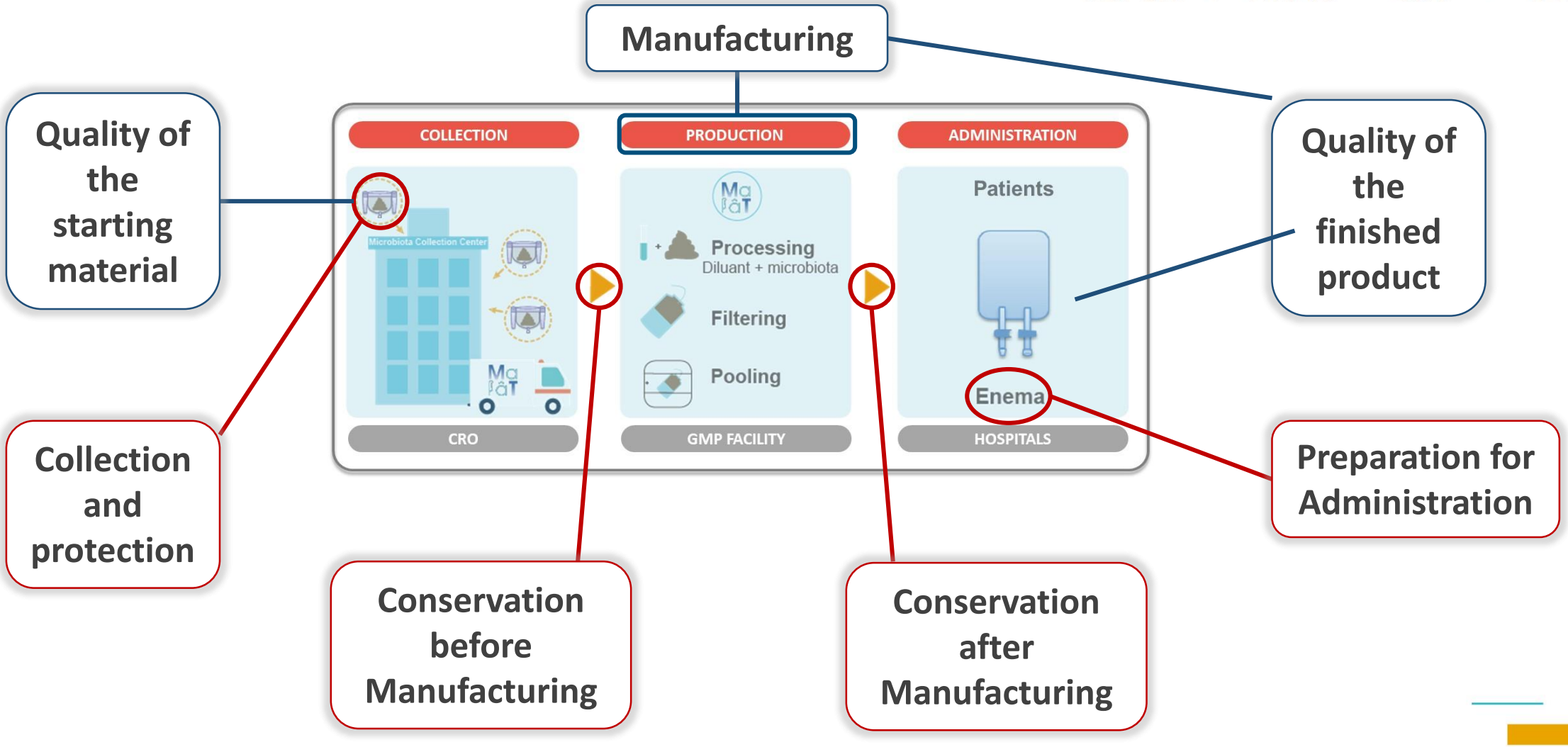
OUR MISSION

- **Lead the development (CMC, Regulatory, Clinical,…) of this new innovative treatment**
- **Develop safe, standardized, and ready-to-use FMT-based drug products at an industrial scale**
- **Bring Approved drugs to the market, meeting Physicians needs**

FMT MANUFACTURING & SUPPLY



CHALLENGES IN FMT MANUFACTURING & SUPPLY



COLLECTION OF SAMPLES & PROTECTION

COLLECTION

COLLECTION DEVICE

- Convenient for donor
- Dedicated to FMT
- Protect against contamination
- Protects against oxidative stress
- Enhance stability and viability
- Patented and CE Marked

QUALITY OF STARTING MATERIAL

- Qualification of donor
- Full screening

PROTECTION BEFORE MANUFACTURING

- **Recommendation in EU**[1] is to prepare the fresh stool within **6 hours** ➔ Extremely restrictive and not compatible with GMP manufacturing of a standard and regulatory approved drug product.

MaaT Pharma demonstrates that :

- Samples stored **at 4°C for 72h** are not substantially affected in term of
  - ❖ **Composition**
  - ❖ **Viability**

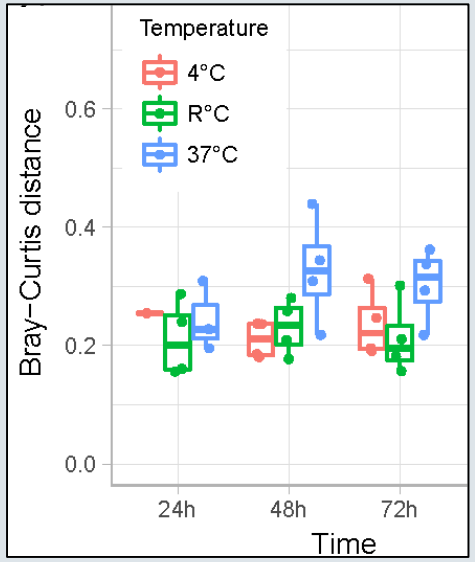
[1] *Cammarota et al. (2017) Gut*

SAMPLE STABILITY AFTER COLLECTION – BEFORE MANUFACTURING

COLLECTION

OTU composition of fresh stools left 24h, 48h or 72h at 3 temperatures.

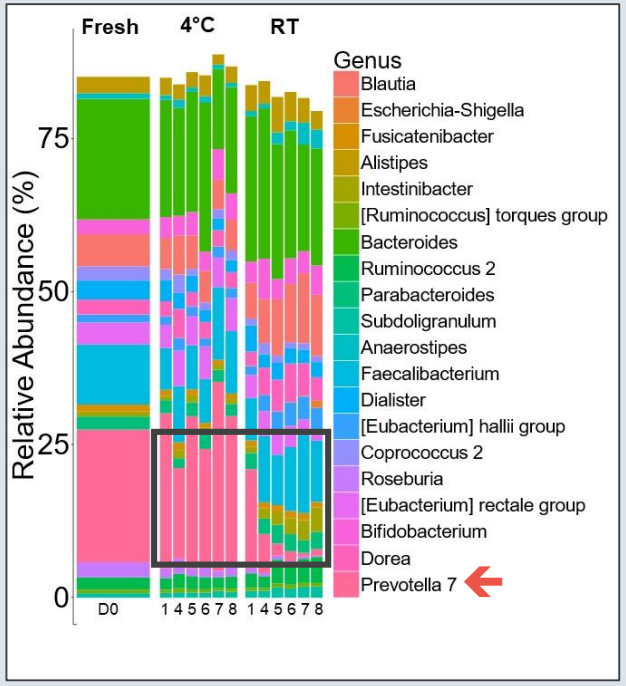
Bray-Curtis distances to baseline showing microbial community shifting over time.



➔ **4°C or RT : No Shift**

➔ **37°C : unfavorable**

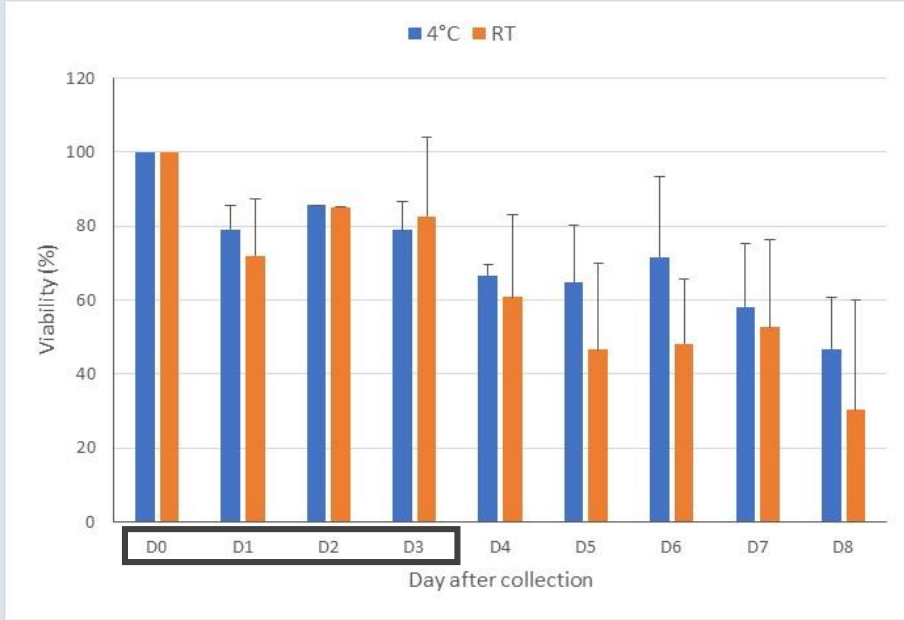
Metagenomic profile of a fresh stool containing a large population of *Prevotella*



➔ **4°C : No Shift**

➔ **RT : Significant decrease of the *Prevotella* genus**

Viability of bacteria in fresh stools stored at 4°C or RT, measured by flow cytometry from Day0 to Day8



➔ **4°C and RT : Viability in fresh stools is still around 80% up to 3 days after collection**

PRODUCTION OF FMT

PRODUCTION

GMP Facility

- **State of the Art**
- **Pioneer and Leader in Europe**
- Unique platform tailored to production of FMT
- Good experience producing IMP for clinical trials

MANUFACTUTING PROCESSES

- **Patented diluent and process**
- **Robust and Reproductible**
- **Scalable**
- **Standardized**
- No exposure of the manipulator with the sample
- No exposure of the sample to the environnement

1st EU GMP Platform

PRODUCTION

Processing
Diluant + microbiota

Filtering

Pooling

GMP FACILITY

FINISHED PRODUCT

- Distribution in 150 mL enema pouches
- Packaging in card box
- **Storage at -80°C**

QUALITY OF FINISHED PRODUCT

- Pooling provide a **rich homogeneous** and reproductible product
- **Quality Control** :
  - ✓ Viability
  - ✓ Diversity

QUALITY OF THE POOLED INOCULUM

PRODUCTION

- **High Richness of the pooled inoculum**

  ➔ Significantly higher than with single donor

- **Homogenous** and **Robust**

- **Diversity** of our drugs is evaluated at **26** (InvSimpson)

  After Hematopoietic Stem Cell Transplantation**, 3 years mortality** is reduced to[1] : 53% when InvSimpson is < 2

  11% when InvSimpson is >4

[1] *Taur et al. (2014) Blood*

STORAGE AND ADMINISTRATION OF THE FROZEN INOCULUM

STORAGE

PROTECTION AFTER MANUFACTURING

Recommendation in EU is to use **Saline solution** for fresh preparation of FMT, and to add 10% **Glycerol** before freezing. [1]

MaaT Pharma patented diluent provides a good stability and quality of the frozen products. After thawing :

- **The revivification potential** is higher
- **The metabolomic fingerprint** is conserved
- **The viability is demonstrated for 18 months**

[1]*Cammarota et al. (2017) Gut*

ADMINISTRATION

Patients

Enema

HOSPITALS

SUPPLY TO HOSPITALS

- Express Transport in dry ice

PREPARATION FOR ADMINISTRATION

Recommendation in EU is to thawed in a warm water bath (37°C) and infused within 6 hours.

For its products MaaT Pharma recommends:

- Thawing at 37°C in water bath for 10 min
- **To avoid prolonged thawing at 37°C (20% viability loss after 30')**
- **To avoid slow thawing at 4 °C**

REGULATORY STATUS OF FMT – NO HARMONIZED POSITION

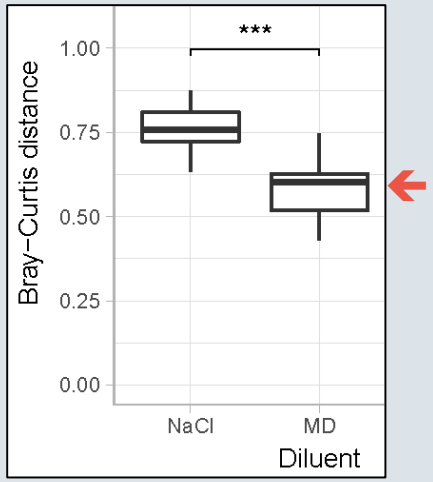
Medicinal Product : FR – GE – UK **Transplantation product :** IT – SP **Biological Drug :** US – CA

QUALITY AND STABILITY USING MAAT PHARMA's PROCESS

STORAGE

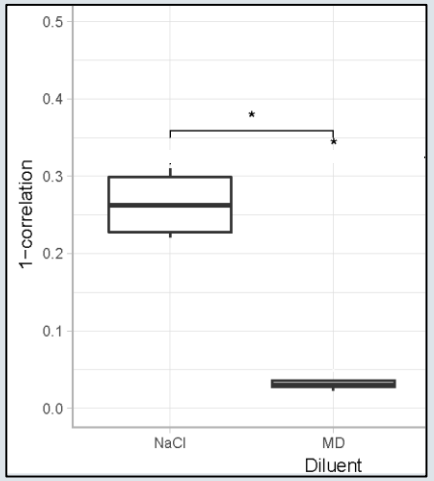
Revivification potential of culturable bacterial communities in FMT prepared with MaaT Pharma diluent (MD) compared to NaCl.

Bray-Curtis distances to baseline (fresh faeces) at the OTU level.



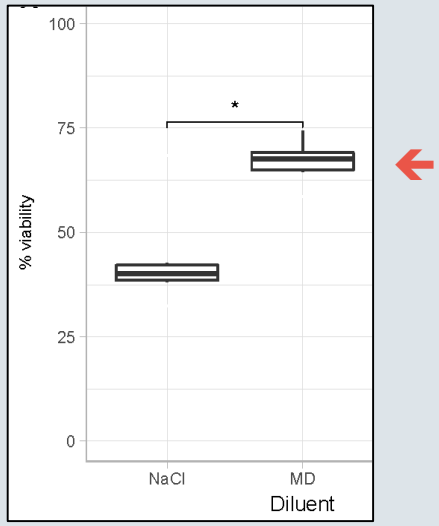
Metabolomic fingerprints of culture of supernatants of transplants prepared with **MaaT Pharma diluent or NaCl**.

Freshly prepared, immediately cultured transplant, served as the reference baseline.



➔ **MaaT Pharma's diluent has a clear cryoprotective effect compare to NaCl**

Viability test by flow cytometry showing percent live bacteria in FMT prepared in **NaCl or MaaT Pharma diluent (MD)**

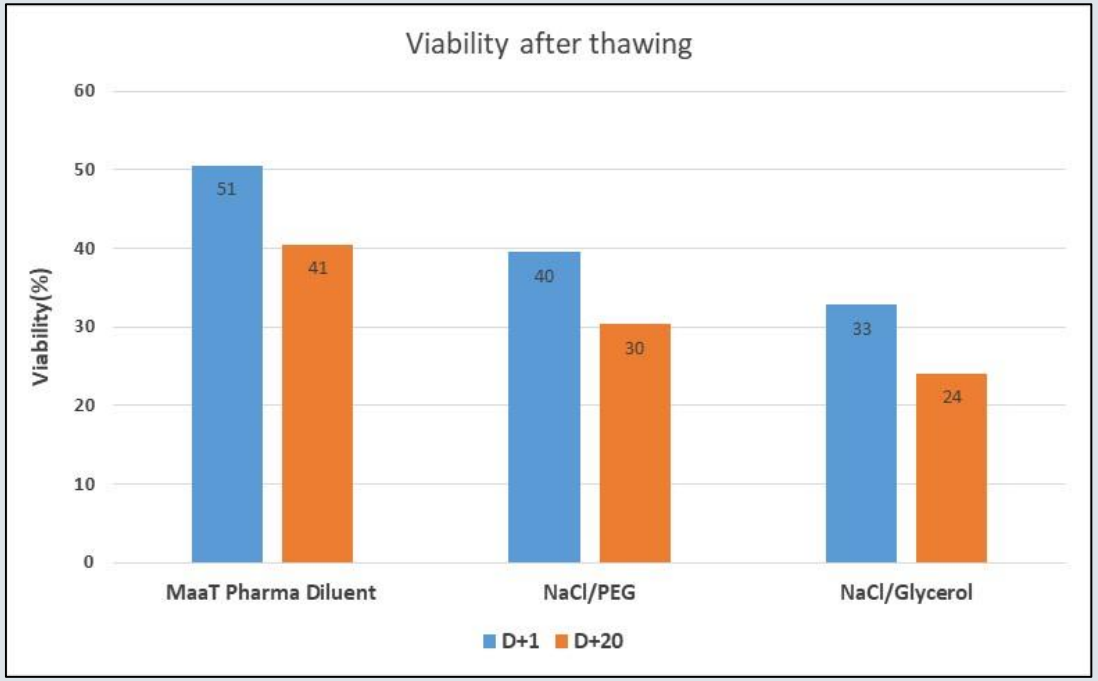


➔ **MaaT Pharma's diluent has a clear cryoprotective effect compare to NaCl**

QUALITY AND STABILITY USING MAAT PHARMA's PROCESS

STORAGE

Viability test by flow cytometry showing percent live bacteria in **FMT** prepared in **MaaT Pharma diluent, NaCl/PEG or NaCl/Glycerol**



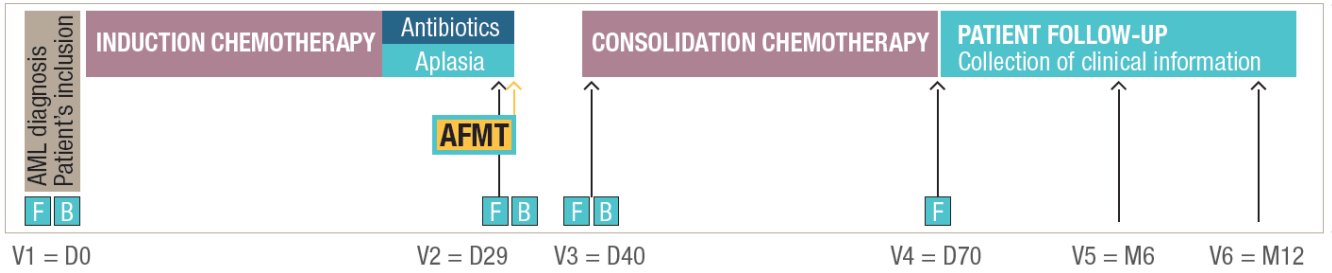
➔ **MaaT Pharma's diluent has the best cryoprotective effect compare to other preparation methods**

CLINICAL PoC ON AML – ODYSSEE STUDY

CLINICAL

Relevant data generated during this first study supports future developments

OdysséE By MaaT Pharma



F: Faeces collection - B: Blood collection

12 months follow up for all patients

June 2018
(Database Lock)

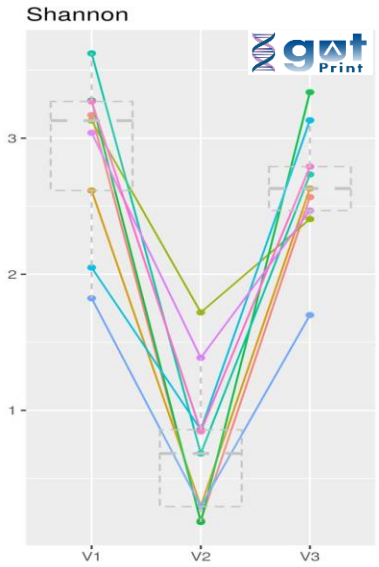


Fig 1: Microbiome Diversity Based on Shannon's Scale

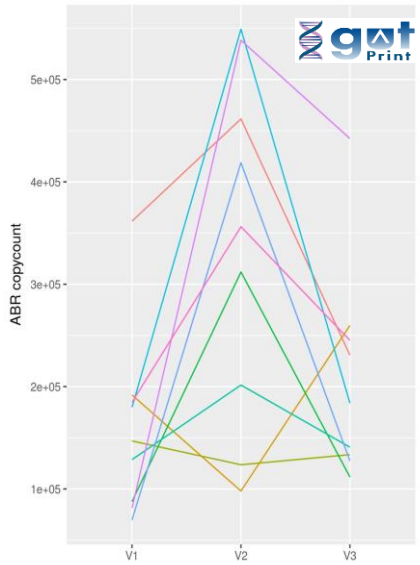


Fig 2: Antibiotic Resistance Gene Copy numbers

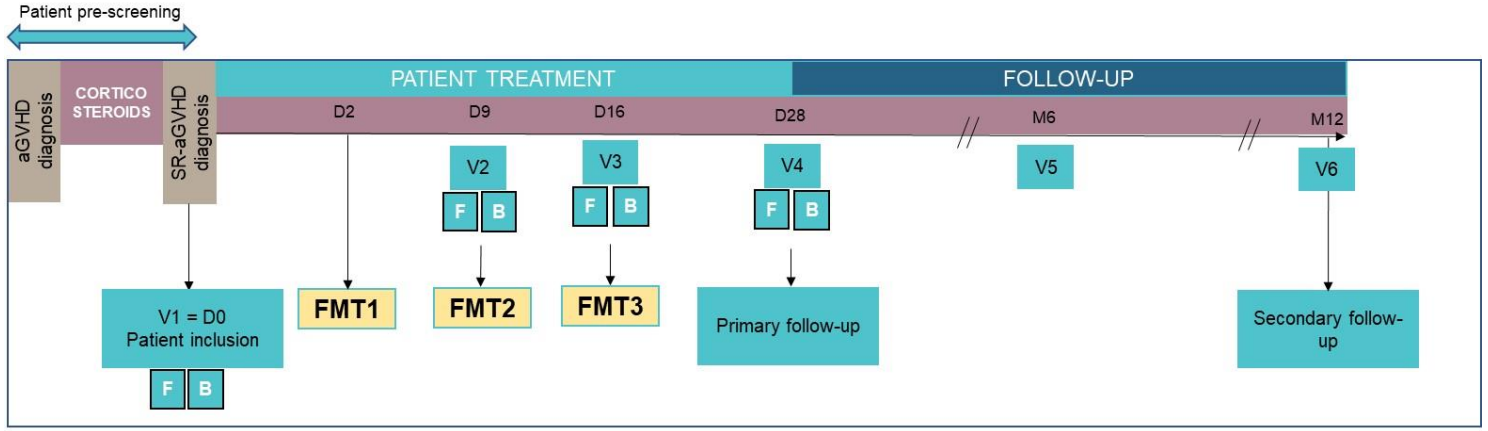
- **25** patients treated with **12 months** follow up
- **Survival after one year: 21/25, ie 84% (historical data: 70%), analysis on going**
- **Feasibility** of FMT procedure
- Primary objective obtained:
  90% Microbiota recovery
  Reduction of **antibio-resistance gene carriage**
- Restoration of the ratio: health promoting / detrimental bacteria

NEW STUDY - HERACLES : POTENTIAL TO REDUCE MORTALITY IN AGVHD

CLINICAL

HERACLES By MaaT Pharma

([NCT03359980](NCT03359980))



At D0, D9, D16 and D28: F B Faeces and Blood Collection (**before** FMT treatment for V2 and V3) – Samples will be sent to a central lab

May 2020

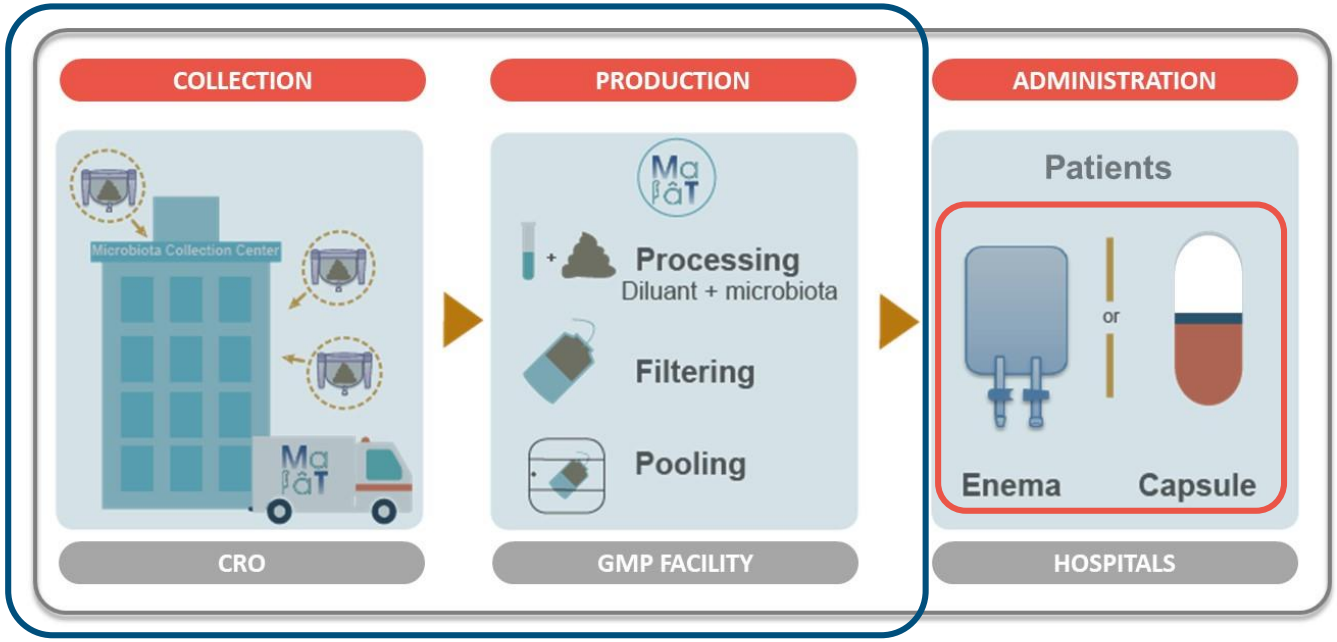
- **International study:** 4 countries, 21 reference centers
- **First controlled trial** evaluating the impact of our Enema form in steroid refractory **aGvHD**
- **Hard endpoint** based on Complete Response and Very Good Partial Response (CR+VGPR)
- Up to one year follow up
- **First patient expected in June 2018**

NEXT GENERATION OF FMT PRODUCTs

NEXT

- The current IMP available from MaaT Pharma is an **Enema.**
- However, based on our knowledge and on our standardized and robust process, we are currently developing a patient-friendly solution (**Capsule**) as an alternative to rectal administration for appropriate patients and/or long term treatment.

Core Process



The rich and homogeneous pool can be either packaged in 150mL **enema pouches** or **lyophilized and encapsulated**

CAPSULE IS THE NEXT GENERATION

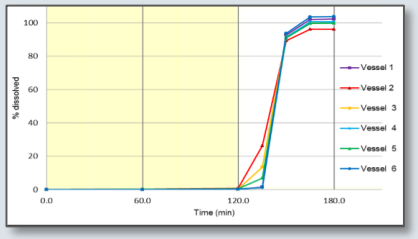
NEXT

Capsule

- Dose: 10^{10} bacteria/capsule
- Ileo-Colonic delivery
- Capsule Size 0
- Shelf life: min 1 year

STANDARD CHARACTERIZATION

- Viability
- Metagenomics
- Dissolution USP2, USP3, USP4 / Desintegration



ADDITIONAL CHARACTERIZATION

- TIM-1 (TNO Gastro-Intestinal Model)
- Bio-relevant dissolution test (stress and physiological dissolution media)
- DGM (Dynamic gastric Model)

OUR NEXT STAGES

- **GMP** Scale Up
- **Clinical** assessment : maintain symbiosis in Leukemia patients

Thank you!

Hervé Affagard

Co-founder and CEO of MaaT Pharma

Innovative committed entrepreneur

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