XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Ruolo del trapianto di microbiota fecale nel trattamento della GvHD acuta intestinale

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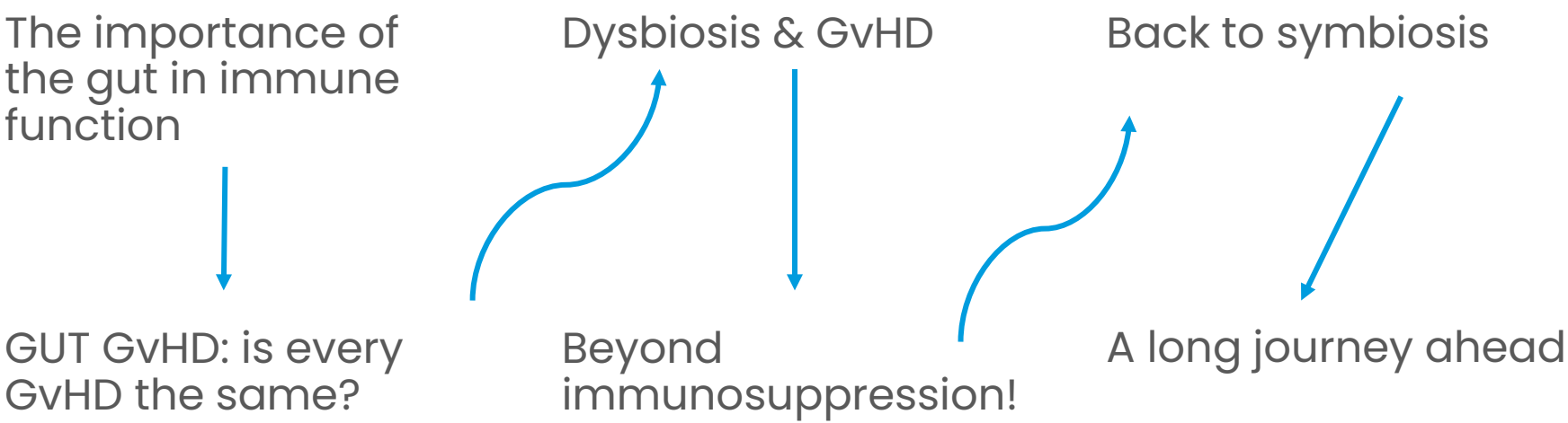
Stem Cell Programme – Ospedale San Raffaele IRCCS

Milano

Disclosures of Maria Teresa Lupo-Stanghellini

Company name	Research support	Employee	**Consultant**	Stockholder	Speakers bureau	**Advisory board**	**Other**
Novartis						**X**	**X**
Mallinckrodt						**X**	**X**
Pfizer						**X**	
Incyte			**X**				**X**
Neovii							**X**
Sanofi			**X**				**X**

Agenda


The importance of the gut in immune function
Dysbiosis & GvHD
Back to symbiosis
GUT GvHD: is every GvHD the same?
Beyond immunosuppression!
A long journey ahead

Human GI 100 trillion microorganism.

Human genome 23000 genes.

600.000 microbial genes and 22x10^6 genes in human GUT microbiome

2 phyla – Bacteroides & Firmicutes - 90% in healthy people

The microbiota and host **coevolve** from birth.

Host–microbiome symbiosis in healthy individuals

Essential functions:

digestive metabolism, barrier function, prevention of the proliferation of environmental microbes stimulation of natural defenses,

development of the intestinal wall,

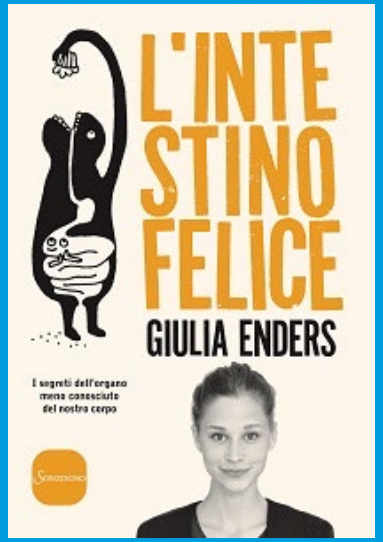
immune system stimulation

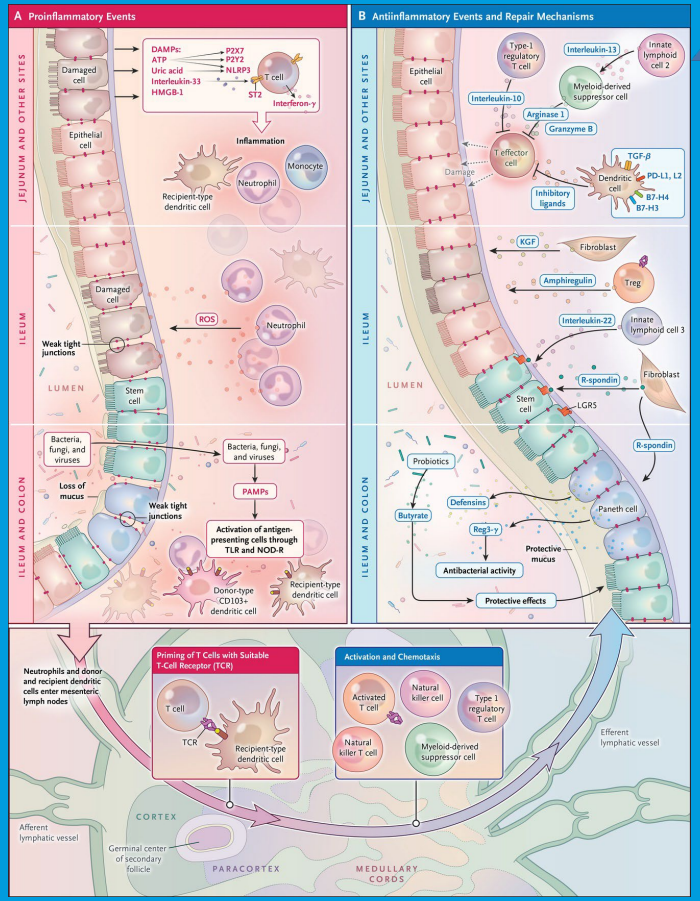
Dysbiosis = alteration of Host / Microbiome symbiosis.

Alteration of GUT barrier → uncontrolled immune response and inflammation.

Overall decrease in microbial richness and diversity
with a loss of beneficial bacteria

Malard, Gaugler and Mothy, Lancet H 2022





Zeiser R, Blazar BR. N Engl J Med ;377:2167-2179

Pro-Inflammatory

DAMP
- ATP,
- **IL33 (ALARMIN)**
-> ST2

PAMP (viruses bacteria fungi)

TNF

IL6

IL1

JAK-STAT pathway

IL10 IDO KGF

Amphiregulin

R-spondin

Butyrate

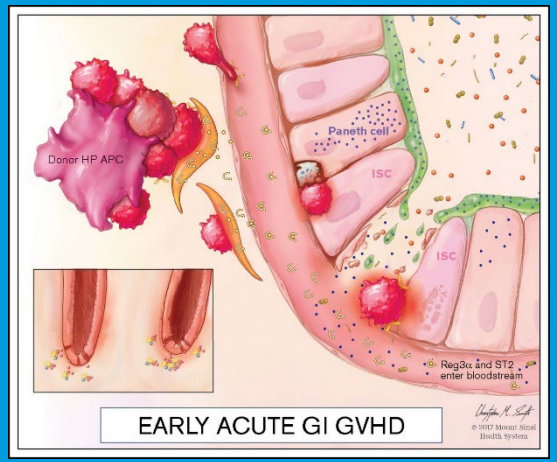
Cryptopatches ->

ILC3 -> **IL22** -> + ICS & Paneth

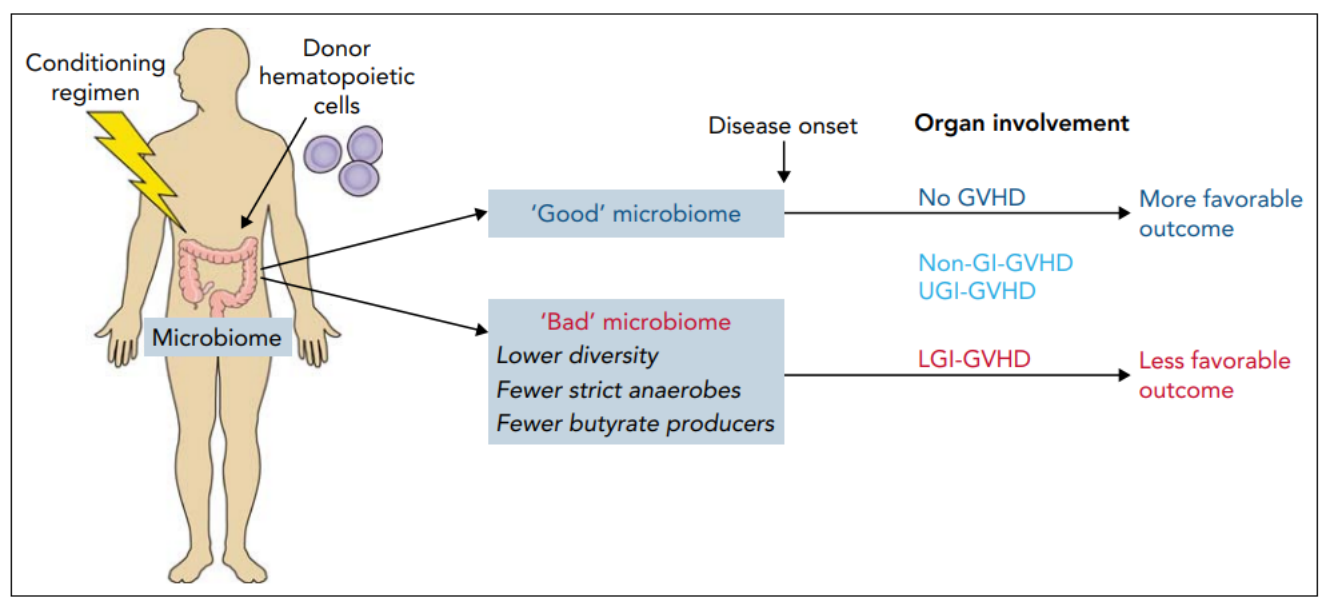
Paneth cell - the guardian of the crypt:

α-defensin + **REG3α**

Anti-Inflammatory



JLM Ferrara & MS Chaaudhry, Hematology 2018

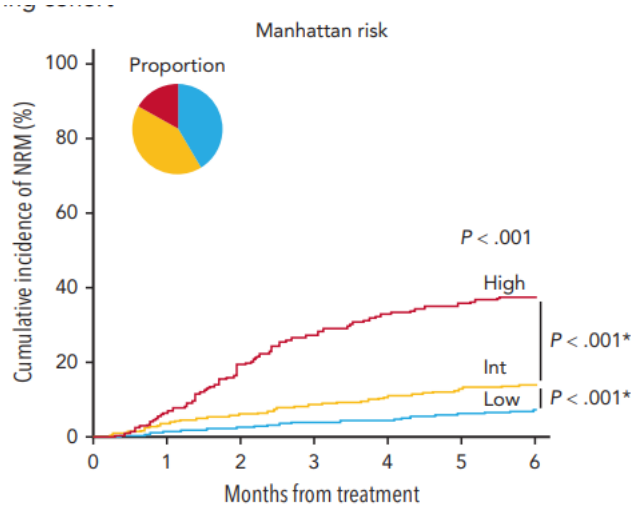

Conditioning regimen
Donor hematopoietic cells
Microbiome
Disease onset
Organ involvement
'Good' microbiome
No GVHD
More favorable outcome
Non-GI-GVHD
UGI-GVHD
'Bad' microbiome
Lower diversity
Fewer strict anaerobes
Fewer butyrate producers
LGI-GVHD
Less favorable outcome

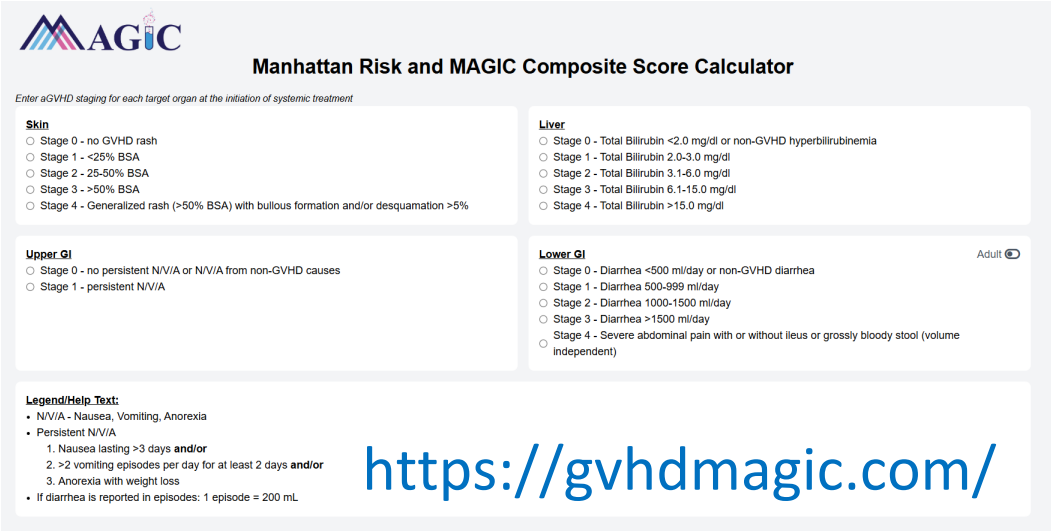
GUT GvHD: is every GvHD the same?

TRANSPLANTATION

Novel MAGIC composite scores using both clinical symptoms and biomarkers best predict treatment outcomes of acute GVHD

Yu Akahoshi,[1] Nikolaos Spyrou,[1] Daniela Weber,[2] Paibel Aguayo-Hiraldo,[3] Francis Ayuk,[4] Chantiya Chanswangphuwana,[5]





https://gvhdmagic.com/

Dysbiosis & GvHD

Biology

Intestinal *Blautia* Is Associated with Reduced Death from Graft-versus-Host Disease

Jenq R et al, BBMT 2015

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

Enteric Microbiome Markers as Early Predictor Clinical Outcome in Allogeneic Hematopoietic Transplant: Results of a Prospective Study in Ac

Nicasio Mancini,[1,2,a] Raffaella Greco,[3,a] Renée Pasciuta,[1] Maria Chiara Barbanti,[3] Giacomo Pini,[1] Olivia Beatrice Morrow,[1] Mara Morelli,[3] Luca Vago,[3] Nicola Clementi,[2] Fabio Giglio,[3] Maria Teresa Lupo Stanghellini,[3] Alessandra Forcina,[3] Laura Infurnari,[1] Sarah Marktel,[1] Matteo Carrabba,[3] Massimo Bernardi,[3] Consuelo Corti,[3] Roberto Burioni,[1,2] Jacopo Peccatori,[3] Maria Pia Sormani,[4] Giu and Massimo Clementi[1,2,b]

TO THE EDITOR:

Microbiome markers are early predictors of a in allogeneic hematopoietic stem cell transpla

Raffaella Greco,[1,*] Rosamaria Nitti,[1,2,*] Nicasio Mancini,[2,3] Renée Pasciuta,[3] Francesca Lorentino,[1] Maria Tere Maria Chiara Barbanti,[1] Nicola Clementi,[3] Fabio Giglio,[1] Daniela Clerici,[1] Sarah Marktel,[1] Andrea Assanelli,[1] Massimo Bernardi,[1] Consuelo Corti,[1] Jacopo Peccatori,[1] Massimo Clementi,[2,3] and Fabio Ciceri[1,2]

Article

https://doi.org/10.1038/s43018-023-00669-x

Bacteria and bacteriophage consortia are associated with protective intestinal metabolites in patients receiving stem cell transplantation

E T Orberg et al, Nat Cancer 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation

J.U. Peled, A.L.C. Gomes, S.M. Devlin, E.R. Littmann, Y. Taur, A.D. Sung, D. Weber,

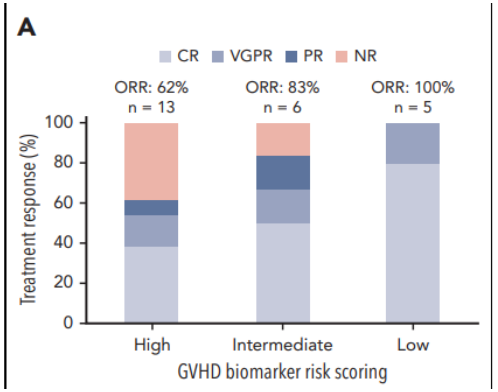
Beyond Immunosuppression

CLINICAL TRIALS AND OBSERVATIONS

A phase 2 study of interleukin-22 and systemic corticosteroids as initial treatment for acute GVHD of the lower GI tract

Doris M. Ponce,[1,2] Amin M. Alousi,[3] Ryotaro Nakamura,[4] John Slingerland,[5] Marco Calafiore,[1] Karamjeet S. Sandhu,[4] Juliet N. Barker,[1,2]

IL-22 is a tissue-protective IL-10–family cytokine - promote mucosal healing and improve intestinal barrier function through non-immunosuppressive mechanisms. Supports enterocyte survival and epithelial regeneration.



ARTICLE OPEN

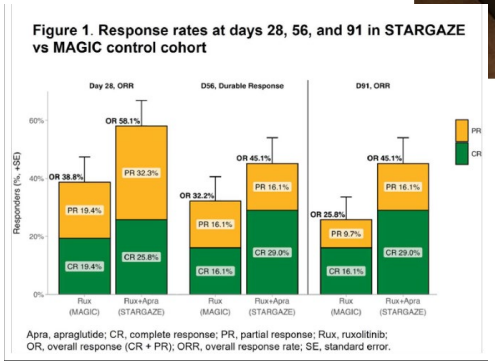
Check for updates

Teduglutide for treatment-refractory severe intestinal acute graft-versus-host disease - a multicenter survey

381 · Volume 31, Issue 2, Supplement , S278-S279, February 2025

The Phase 2 Stargaze Trial of the Glucagon-like Peptide 2 (GLP-2) Analog Apraglutide in Combination with Ruxolitinib for Steroid-Refractory Gastrointestinal (GI) Acute Graft-Versus-Host Disease (aGvHD): Comparisons with a MAGIC Control Cohort

Robert Zeiser, MD [1] · James L.M. Ferrara, MD, DSc [2] · Ioannis Evangelos Louloudis, MD [2] · ... ·



Back to symbiosis: FMT

The tolerance of beneficial commensal bacteria, living symbiotically with our microbiota, is crucial for the intestinal immune system.

In HSCT, intestinal microbiota is damaged (conditioning regimens, antibiotics, chemotherapy, nutritional changes).

Loss of microbiota diversity = predictive factor of HSCT outcome and steroid-refractoriness in patients with GI-aGvHD.

KujawskaJ, Zeiser R and Gil L, Annals Hem 2025

Back to symbiosis
FMT

FMT Delivery

Upper gut (oral intake, nasogastric tube, esophagogastroduodenoscopy, enteroscopy),

Midgut (nasojejunal/enteral tube, jejunostomy, or percutaneous endoscopic cecostomy).

Lower gut (enteroscopy, transendoscopic enteral tube, enema, and **colonoscopy**).

No insufficient evidence to recommend a specific route of FMT administration.

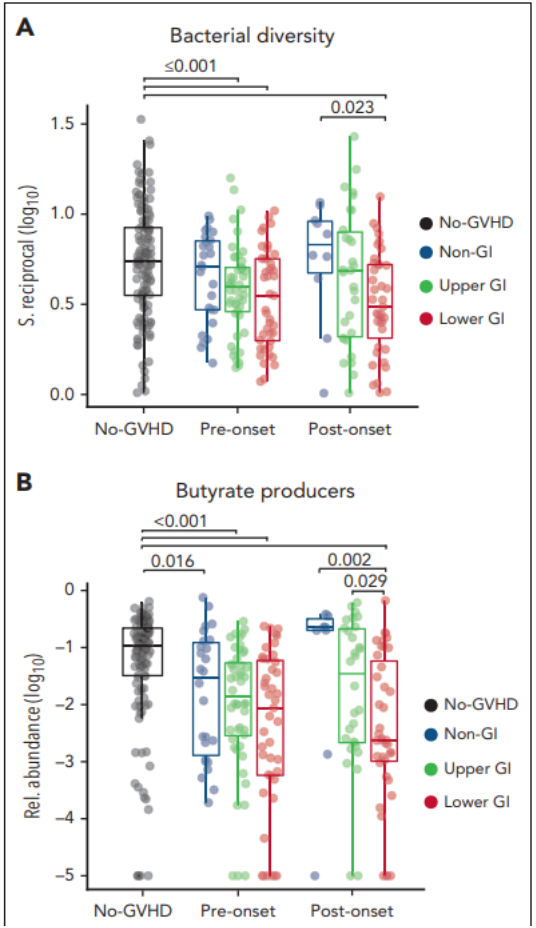
!!!
capsule form
more accessible
less invasive

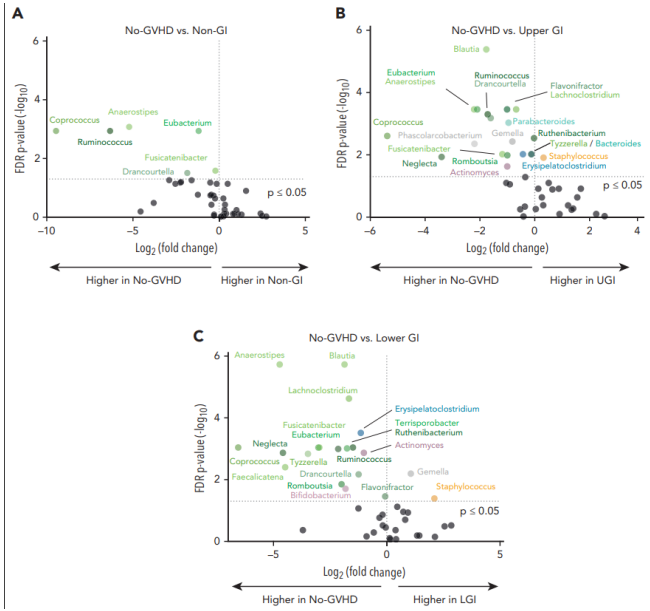
KujawskaJ, Zeiser R and Gil L, Annals Hem 2025

Back to symbiosis

Preservation of the fecal microbiome is associated with reduced severity of GvHD

M Da Burgos Silvas et al, Blood 2022



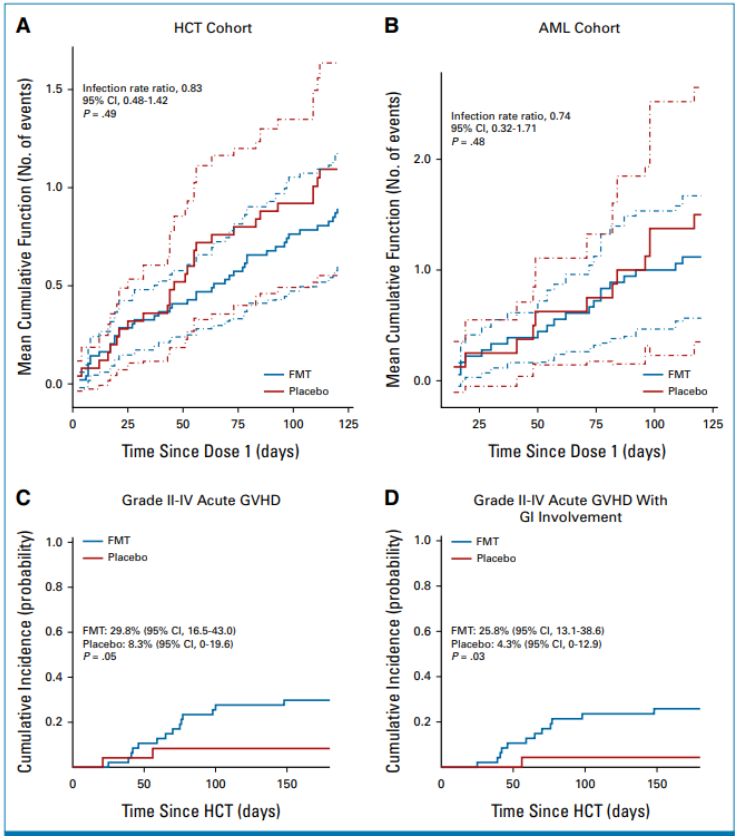


Patterns of microbial dysbiosis can be detected in fecal samples of GI aGVHD patients peri-aGVHD onset.
Markers of microbial health pre-GVHD onset are associated with longer survival and lower risk of GVHD related mortality after allo-HCT.

Back to symbiosis

Randomized Double-Blind Phase II Trial of Fecal Microbiota Transplantation Versus Placebo in Allogeneic Hematopoietic Cell Transplantation and AML

A Rashidi et al, JCO 2023



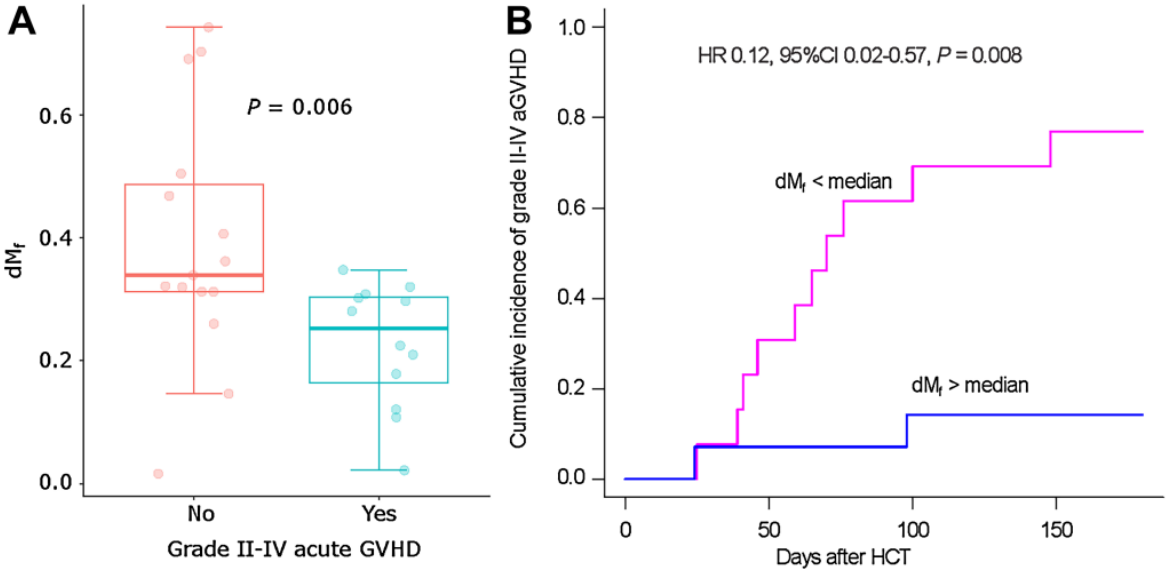
*Randomized phase II trial of **oral, encapsulated**, third-party FMT versus placebo, at the time of neutrophil recovery.*

In allogeneic HCT recipients and patients with AML, third-party **FMT** was safe and ameliorated intestinal dysbiosis, but **did not decrease infections**.

Back to symbiosis

Potential of Fecal Microbiota Transplantation to Prevent Acute GVHD: Analysis from a Phase II Trial

A Rashidi et al, CCR 2023



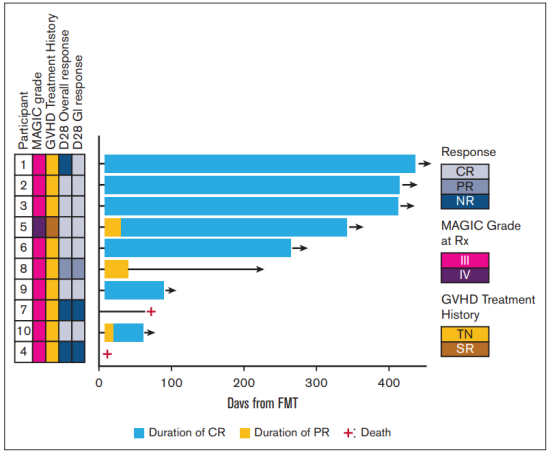
*Randomized phase II trial of **oral encapsulated,** third-party FMT versus placebo, at the time of neutrophil recovery.*

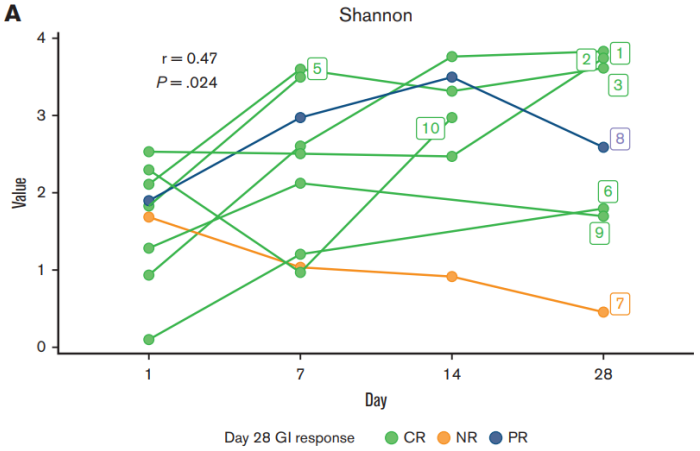
The cumulative incidence of grade II–IV aGVHD by day 180 was lower in the group with greater-than-median dMf than the group with less-than-median dMf [14.3% vs 76.9%, P 0.008]

Back to symbiosis

Third-party fecal microbiota transplantation for high-risk treatment-naïve acute GVHD of the lower GI tract

DeFilipp Z et al, Blood Advances 2024



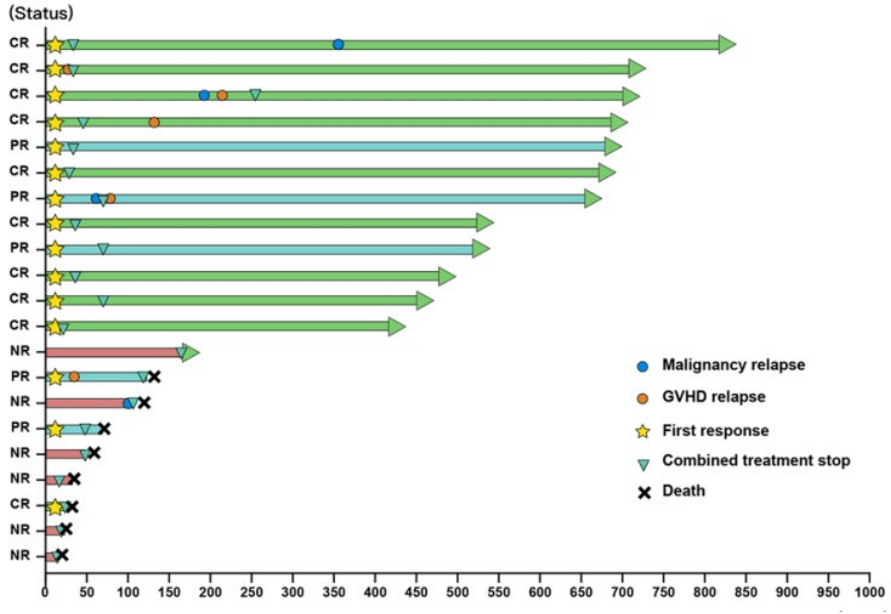


Open-label, single-arm, pilot study, third-party, single-donor FMT in combination with systemic corticosteroids to participants with high-risk acute LGI GVHD, focus on treatment-naïve case

Participants were scheduled to receive 1 induction dose (15 capsules per day for 2 consecutive days), followed by 3 weekly maintenance doses, consisting of 15 capsules per dose

FMTcombined with ruxolitinib as a salvage treatment for intestinal steroid-refractory acute GVHD

Liu et al, Exp Hem & Onc 2022

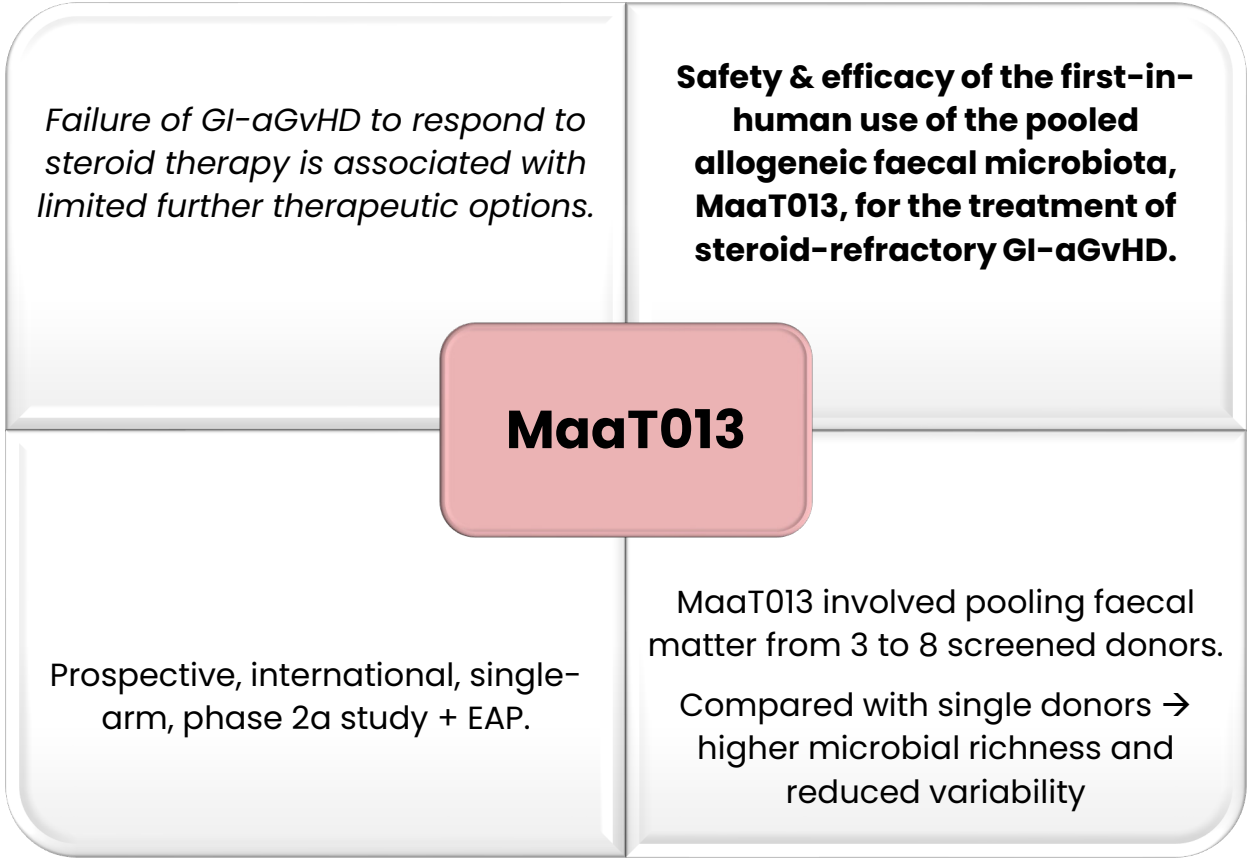


21 patients
FMT + ruxolitinib = salvage treatment GUT SR-aGVHD
Day 28 ORR 71.4% (95% CI 50.4–92.5%) -10 CR.
Day 56 DOR 80%.
GVHD relapse rate 33.3% in responders

Back to symbiosis

Pooled allogeneic faecal microbiota MaaT013 for SR-GI-a-GvHD: a single-arm, multicentre phase 2 trial

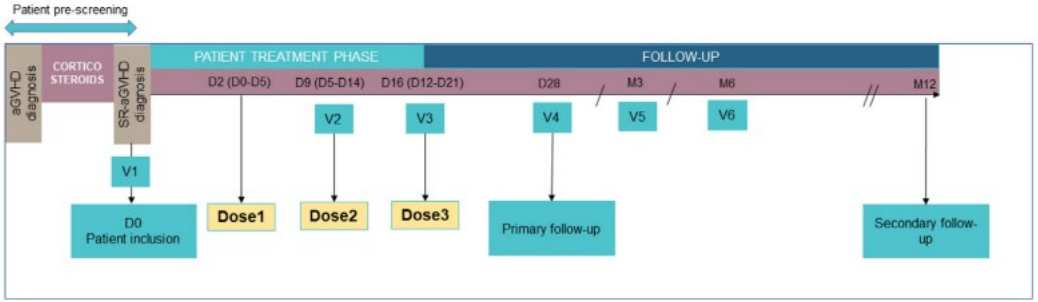
Malard F et al, Lancet 2023



Back to symbiosis

Pooled allogeneic faecal microbiota MaaT013 for SR-GI-a-GvHD: a single-arm, multicentre phase 2 trial

Malard F et al, Lancet 2023



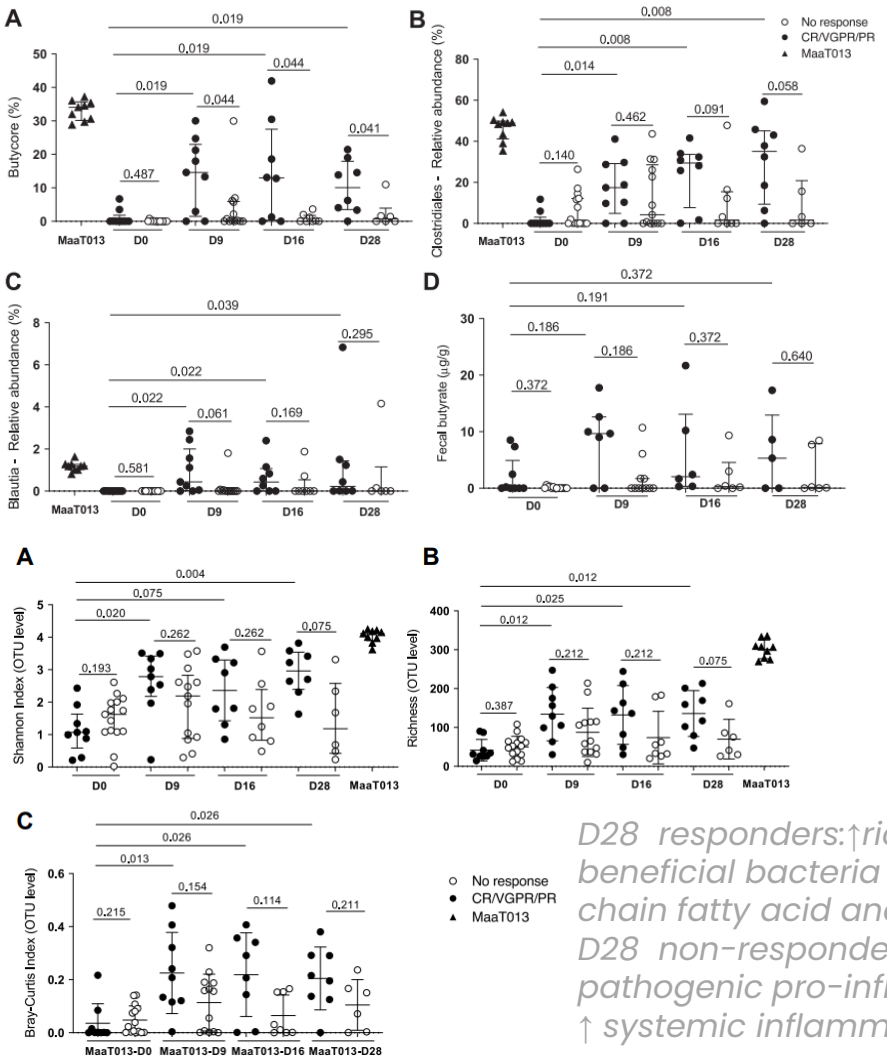
	HERACLES 24 PTS	EAP 52 PTS
D28 ORR	38% 5 CR – 2 VGPR – 2 PR	58% 17 CR - 9 VGPR - 4 PR
12M OS	25%	38%

Safety → Shotgun sequencing analyses of the identified strains suggest that none were found in MaaT013.

Back to symbiosis

Pooled allogeneic faecal microbiota MaaT013 for SR-GI-a-GvHD: a single-arm, multicentre phase 2 trial

Malard F et al, Lancet 2023



D28 responders:↑richness,↑levels of beneficial bacteria + ↑levels of short-chain fatty acid and bile acids.
D28 non-responders:↑ levels of pathogenic pro-inflammatory bacteria & ↑ systemic inflammatory parameter

Back to symbiosis

Phase 3 ARES Study Evaluating MaaT013 in acute Graft-versus-Host Disease

Preliminary Results – Jan 2025

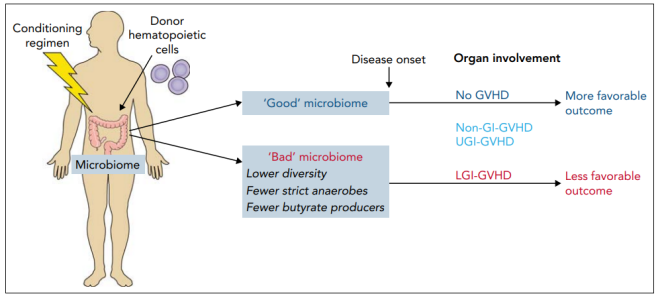
ARES, a pivotal, single-arm, open-label, multicenter European Phase 3 study evaluating the efficacy and safety of MaaT013 in GI-aGvHD in third-line treatment, meaning refractory to steroids and refractory or intolerant to ruxolitinib

	66 pts (50 Eu sites)
F/M	47% / 53%
Median Age	55y (24-76)
aGvHD G2 aGvHD G3 aGvHD G4	9.1% 57.6% 33.3%
Steroid Refractory Steroid Dependent Ruxolitinib Refractory	86.4% 13.6% **100%**

	Outcome
Day 28 GI ORR	**62%** CR 38% / VGPR 20%
Day 28 ORR	64% CR 36% / VGPR 18%
12M OS	54% **Resp 67% / NR 28%**

Data Safety Monitoring Board: no safety concern, efficacy confirmed, positive benefit/risk ratio.

A long (interesting and exciting) journey ahead



FMT

FMT

Staging of symptoms of acute GVHD

Skin manifestation
Yes
Gut or liver manifestation
No
Stage 1–2 (<50%)
Stage 3–4 (≥50%)
Topical steroid alone
Treatment failure
No
Yes
Yes
Gut and/or liver manifestation
Yes
Methylprednisolone
Treatment failure
Ruxolitinib

Treatment failure
- Alemtuzumab
- α1-Antitrypsin
- Anti-IL-2 receptor antibodies
- Anti-TNF
- Antithymocyte globulin
- Extracorporeal photopheresis
- Faecal microbiota transplantation
- Mesenchymal stromal cells
- Methotrexate
- Mycophenolate mofetil
- Pentostatin
- Sirolimus
- Vedolizumab

GLP-2

FMT

IL22

hMSC

Malard et al, NatRev 2023

Advanced Level Bonsai University, March 2025

Grazie

Stem Cell Programme at San Raffaele Hospital