# Gut Biome and Graft-versus-Host-Disease: Do Organisms in the Gut Contribute to GVHD?

## Celebrating a Second Chance at Life Survivorship Symposium

April 27 – May 3, 2024

**Robert Jenq MD**
Director of MD Anderson Microbiome Core Facility and Associate Professor in the Department of Genomic Medicine, MD Anderson Cancer Center

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# Gut Biome and GVHD: Do organisms in the gut contribute to GVHD?

Robert Jenq, MD

May 2, 2024

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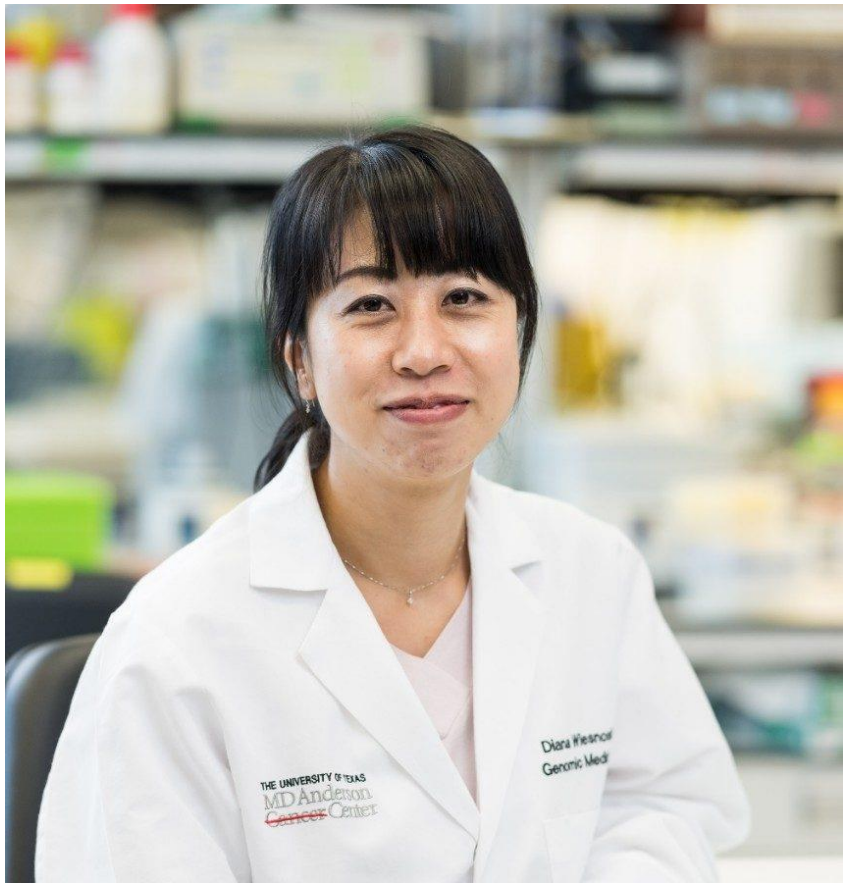
# Disclosures

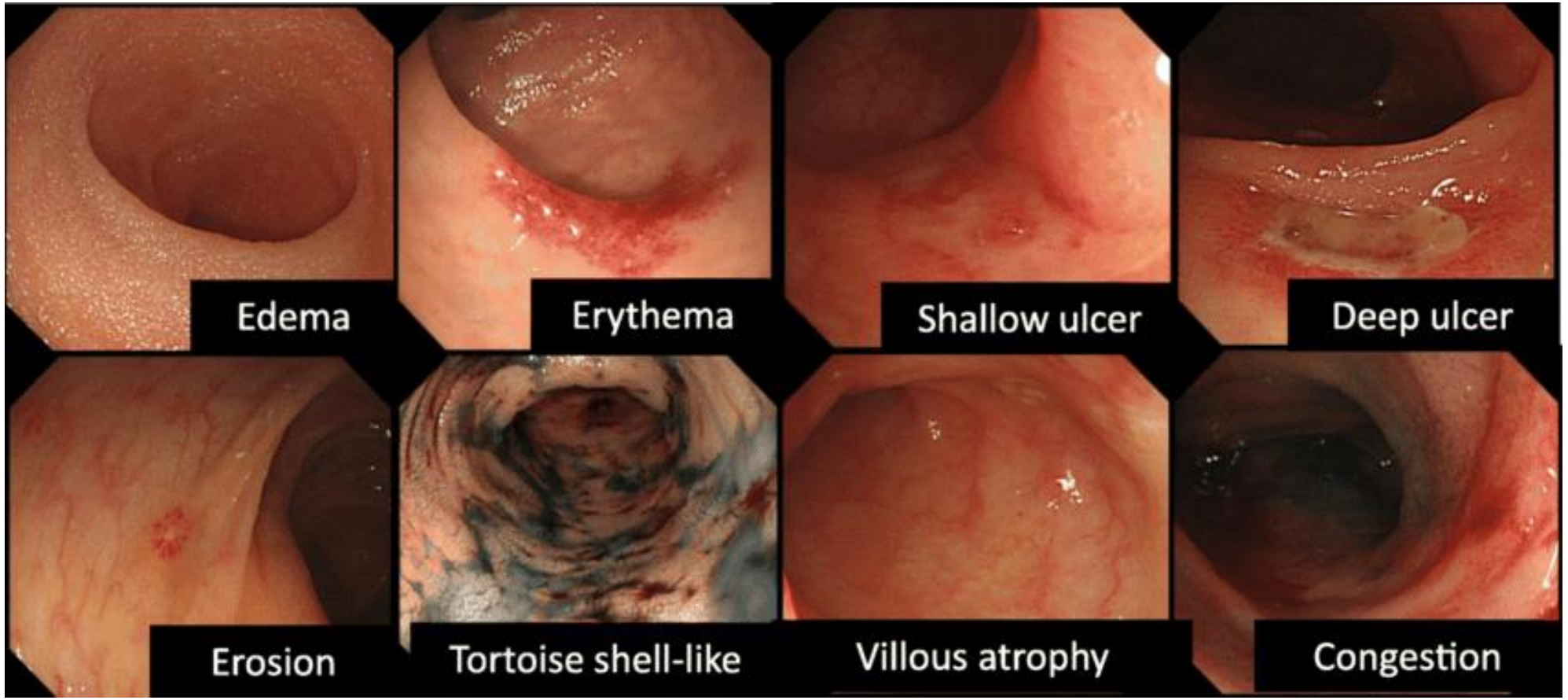
- Advisory board for LISCure Biosciences, Maat Pharma, Prolacta Biosciences, and Seres Therapeutics
- Royalties from Seres Therapeutics

# Acknowledgements

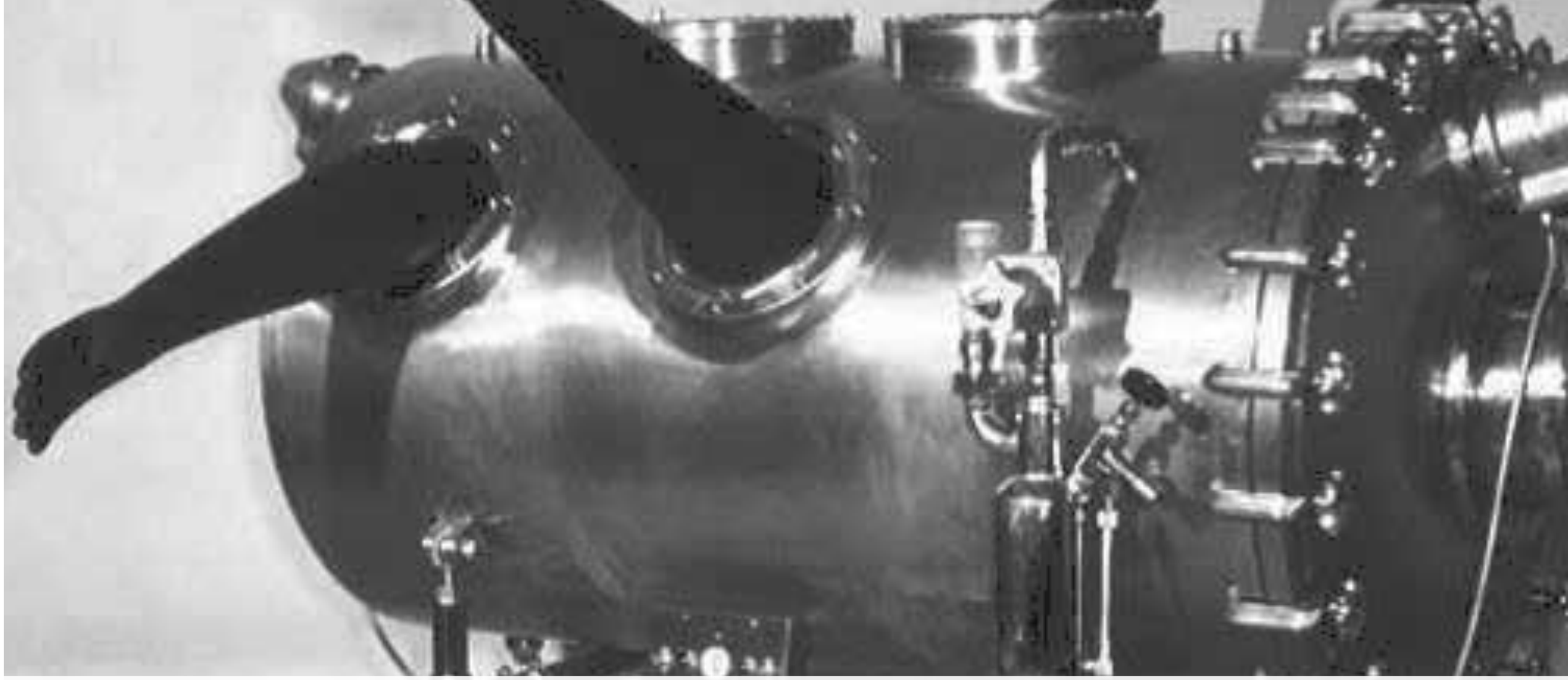




*Cell, 2022 Hayase, et al*
*Unpublished work, in revision*

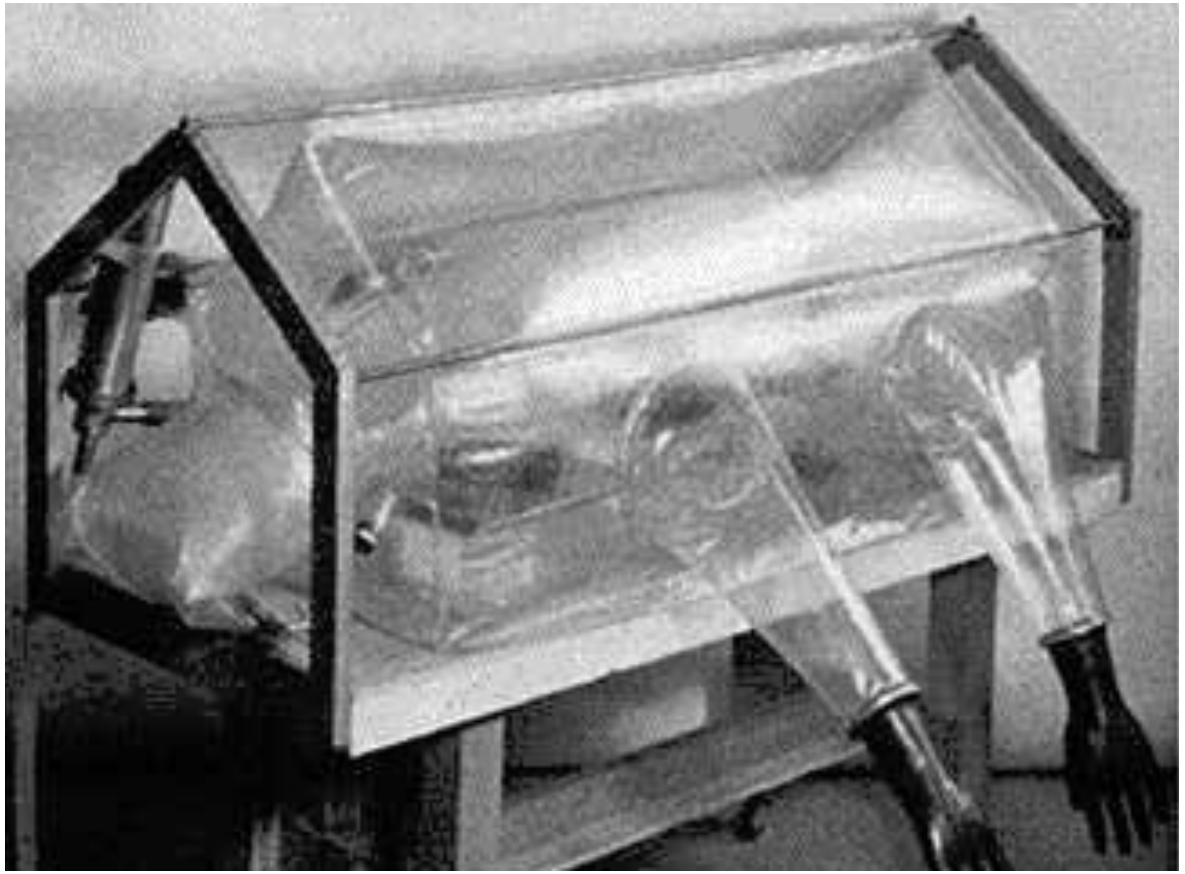
# Colonoscopy Findings in Acute GI GVHD




*Sugihara, et al, BMC Gastroenterology 2018*



Steam sterilizable metal isolator
(Notre Dame University, 1928)



1962 Trexler isolator

2021 Class Biologically Clean (CBC) flexible film isolators

www.cleanairandcontainment.com

flexiblefilmisolators.com

# Bacteria contribute to the development of GVHD

**Mortality and Gross Pathology of Secondary Disease in Germfree Mouse Radiation Chimeras**[1]

1971

J. MIRIAM JONES[2], RAPHAEL WILSON, AND PATRICIA M. BEALMEAR

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1971

**Mitigation of Secondary Disease of Allogeneic Mouse Radiation Chimeras by Modification of the Intestinal Microflora** [1]

D. W. van Bekkum, J. Roodenburg, P. J. Heidt, *and* D. van der Waaij [2]

1974

Fred Hutch transplantation clinic in the 1980s

www.fredhutch.org/

# Controversies in Intestinal Bacterial Decontamination in Allo-HCT

- Clinical studies initially suggested a benefit from near-total bacterial decontamination (Storb et al., 1983)
- Later studies, however, showed no clear benefit (Peterson et al., 1987; Passweg et al., 1998; Russell et al., 2000).

The NEW ENGLAND JOURNAL of MEDICINE

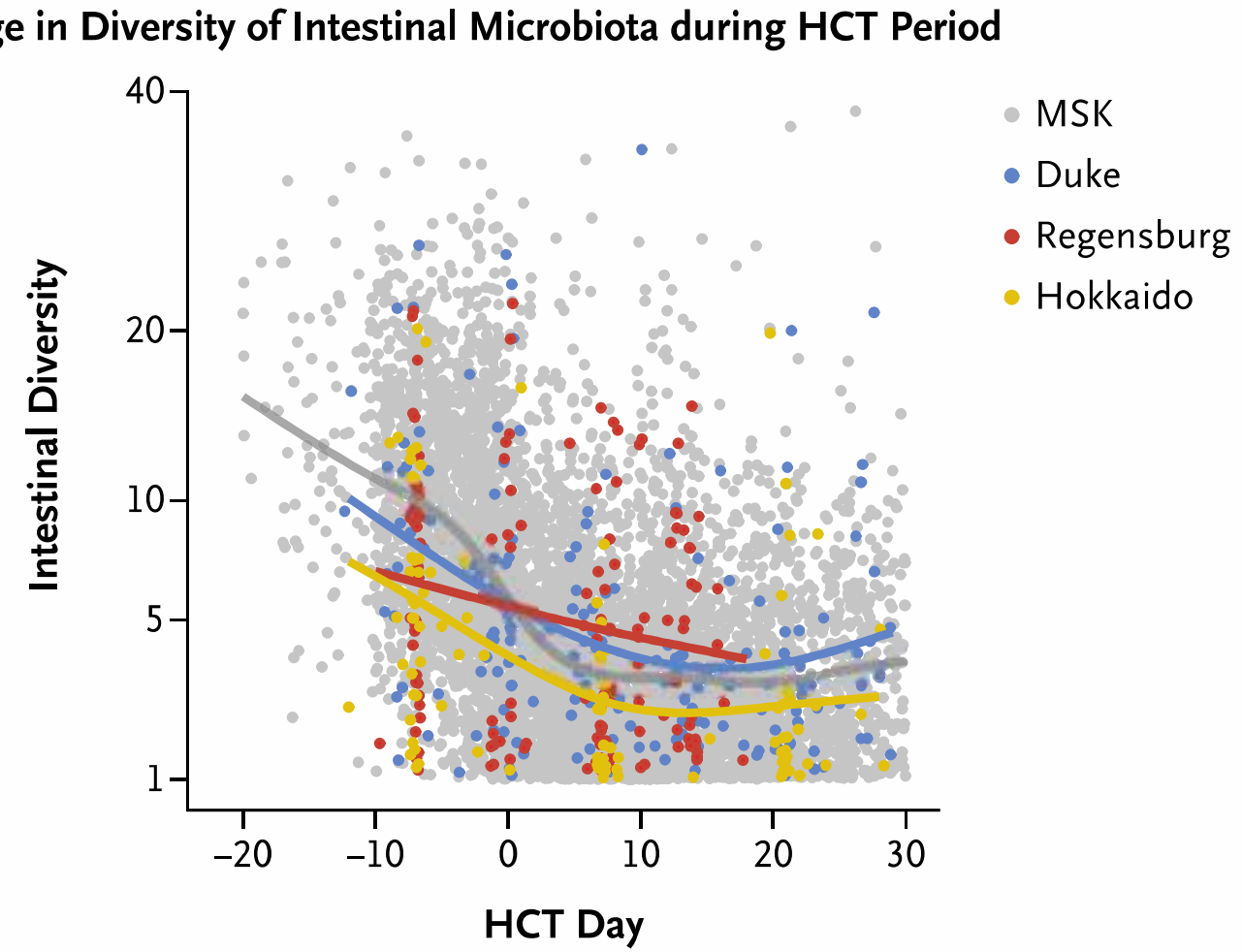
ORIGINAL ARTICLE

# Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation

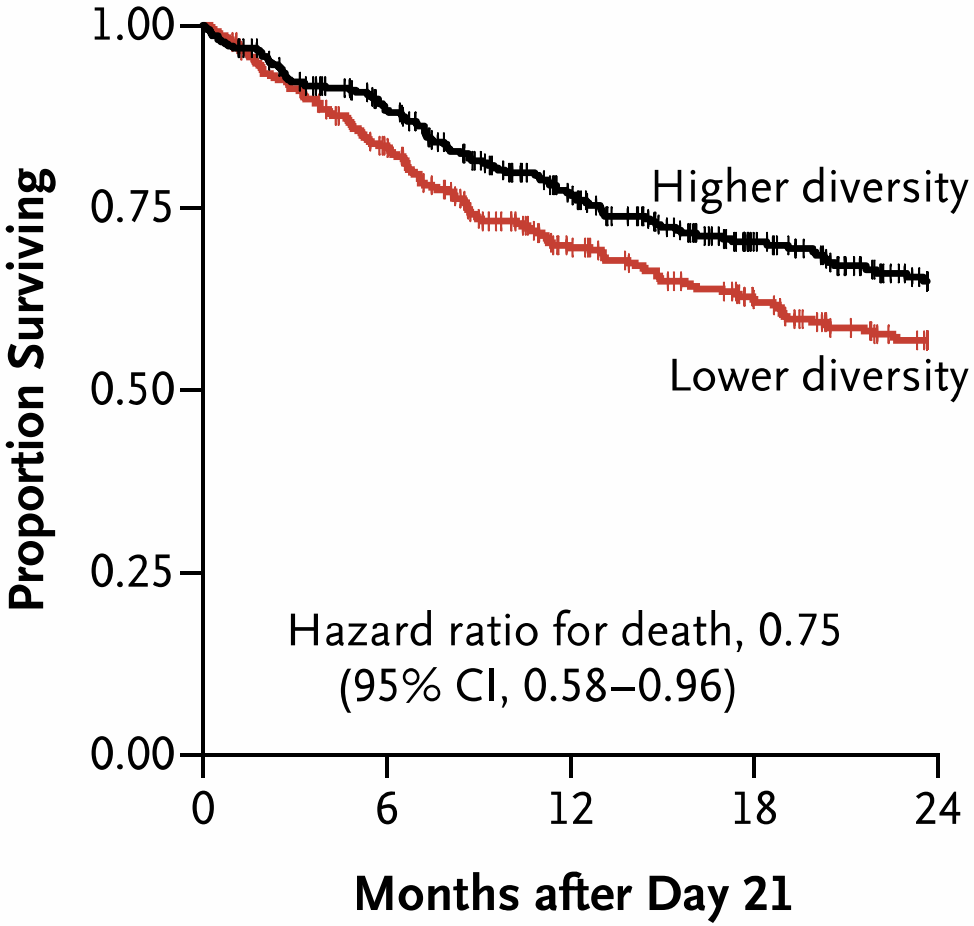
J.U. Peled, A.L.C. Gomes, S.M. Devlin, E.R. Littmann, Y. Taur, A.D. Sung, D. Weber, D. Hashimoto, A.E. Slingerland, J.B. Slingerland, M. Maloy, A.G. Clurman, C.K. Stein-Thoeringer, K.A. Markey, M.D. Docampo, M. Burgos da Silva, N. Khan, A. Gessner, J.A. Messina, K. Romero, M.V. Lew, A. Bush, L. Bohannon, D.G. Brereton, E. Fontana, L.A. Amoretti, R.J. Wright, G.K. Armijo, Y. Shono, M. Sanchez-Escamilla, N. Castillo Flores, A. Alarcon Tomas, R.J. Lin, L. Yáñez San Segundo, G.L. Shah, C. Cho, M. Scordo, I. Politikos, K. Hayasaka, Y. Hasegawa, B. Gyurkocza, D.M. Ponce, J.N. Barker, M.-A. Perales, S.A. Giralt, R.R. Jenq, T. Teshima, N.J. Chao, E. Holler, J.B. Xavier, E.G. Pamer, and M.R.M. van den Brink

## RESULTS

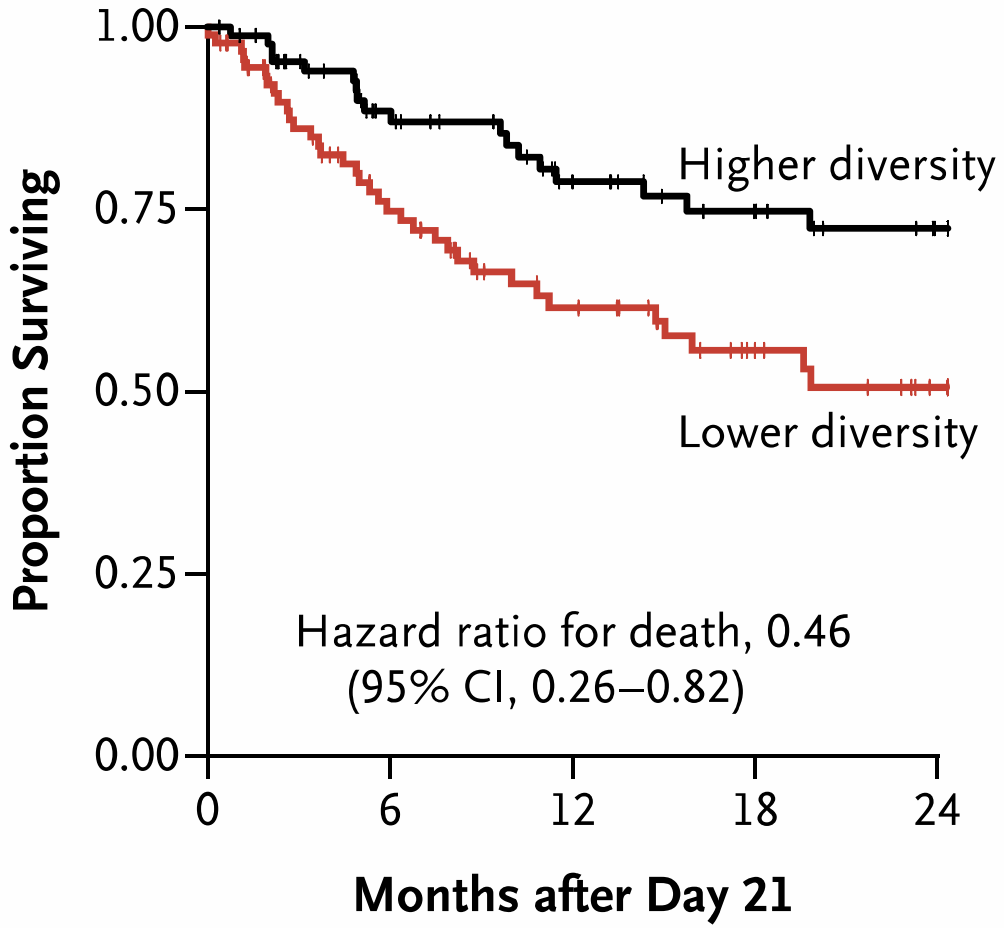
We profiled 8767 fecal samples obtained from 1362 patients undergoing allogeneic hematopietic-cell transplantation at the four centers

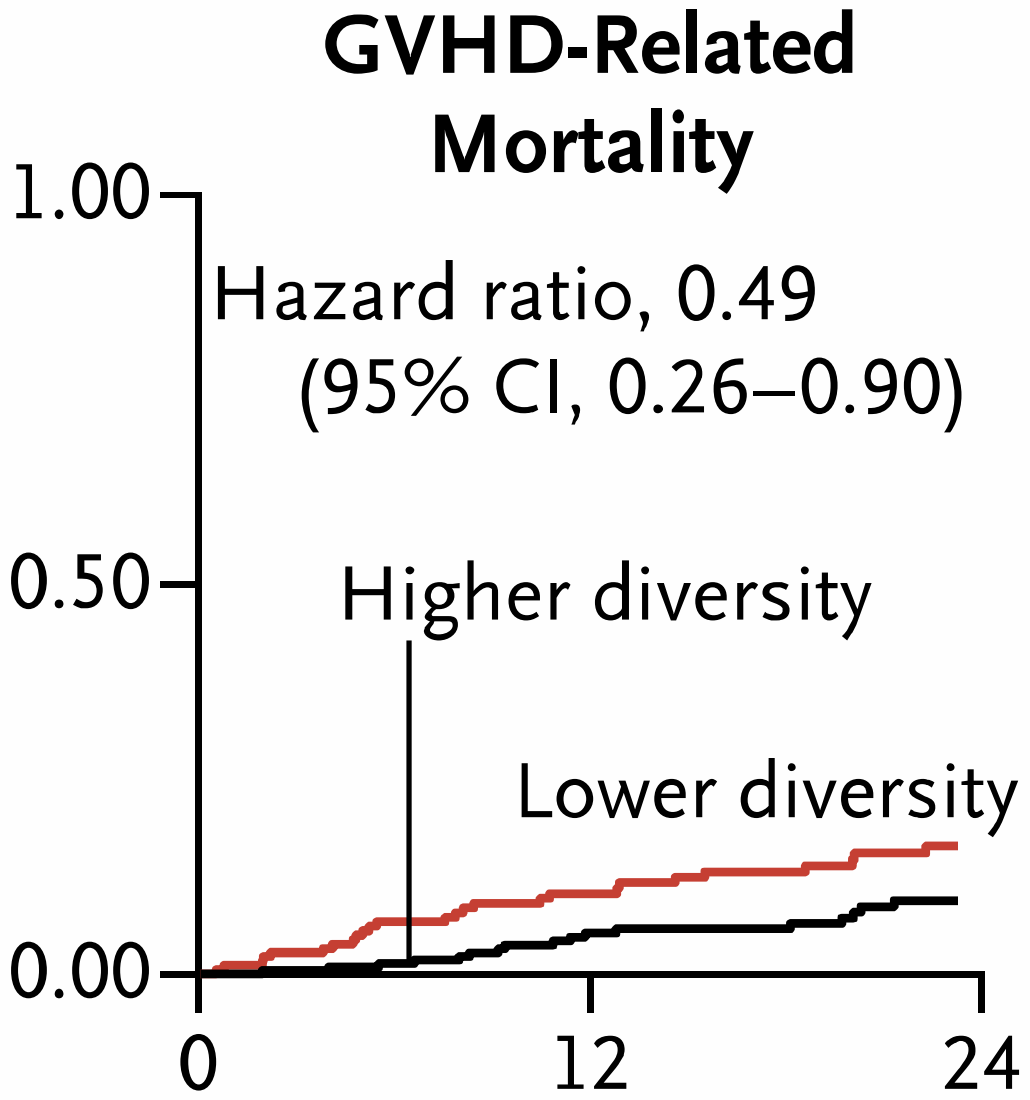


## Overall Survival — Cohort 1



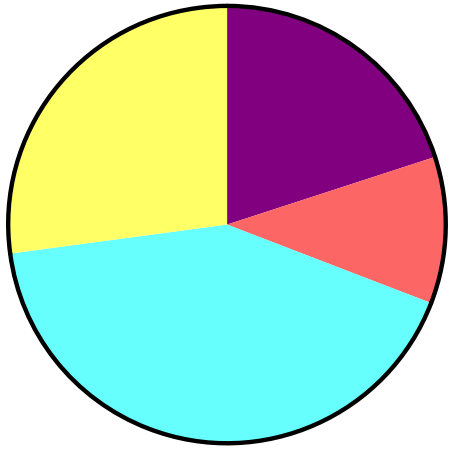

## Overall Survival — Cohort 2




GVHD-Related Mortality
1.00
0.50
0.00
Hazard ratio, 0.49
(95% CI, 0.26–0.90)
Higher diversity
Lower diversity
0
12
24

| | MSKCC<br>Estimate ± S.E. | Regensburg<br>Estimate ± S.E. | Duke<br>Estimate ± S.E. | Hokkaido<br>Estimate ± S.E. |
|---|---|---|---|---|
| Δt | **-0.33 ± .02** | -0.10 ± 0.17 | **-0.15 ± 0.06** | -0.01 ± 0.06 |
| cefepime | 0.07 ± .07 | - | -0.13 ± 0.22 | 0.18 ± 0.19 |
| doripenem | - | - | - | 0.11 ± 0.23 |
| meropenem | 0.08 ± 0.21 | -0.02 ± 0.24 | -0.51 ± 0.33 | **-0.36 ± 0.15** |
| piperacillin-tazobactam | **-0.13 ± 0.05** | -0.24 ± se 0.29 | -0.35 ± 0.28 | - |
| teicoplanin | - | - | - | -0.15 ± 0.12 |

# Cohort of 295 patients with AML or MDS who underwent allogeneic HCT at MD Anderson



Total=295

- No antibiotics
- Cefepime
- Meropenem
- Both meropenem and cefepime

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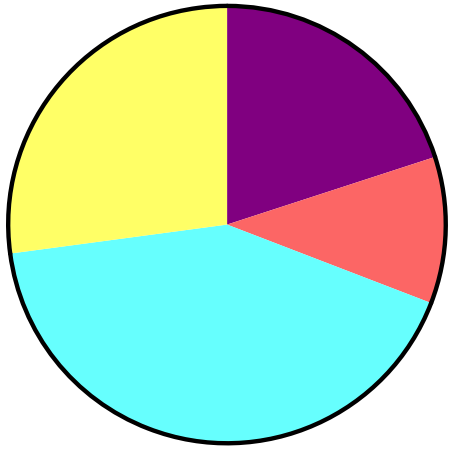

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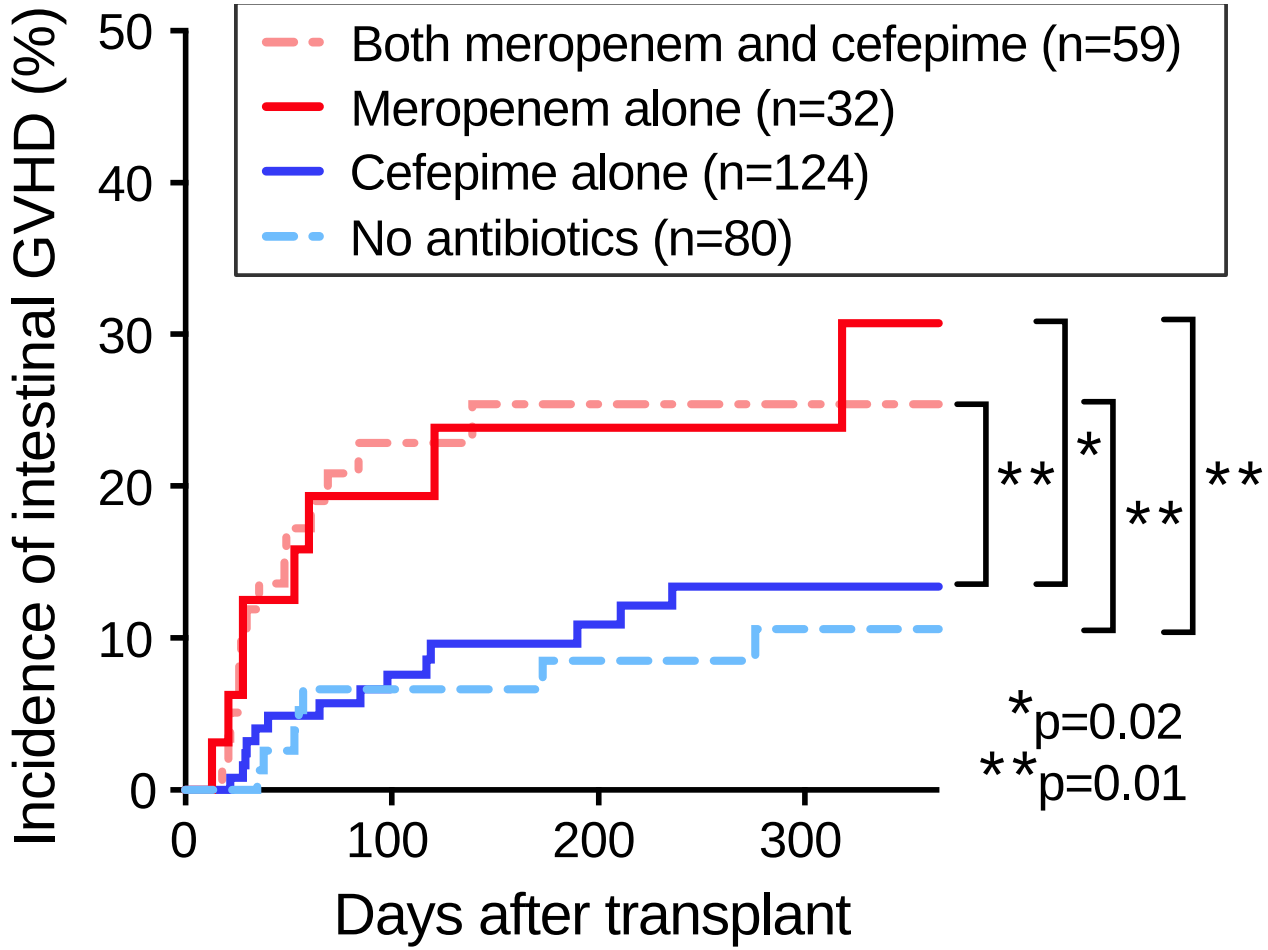
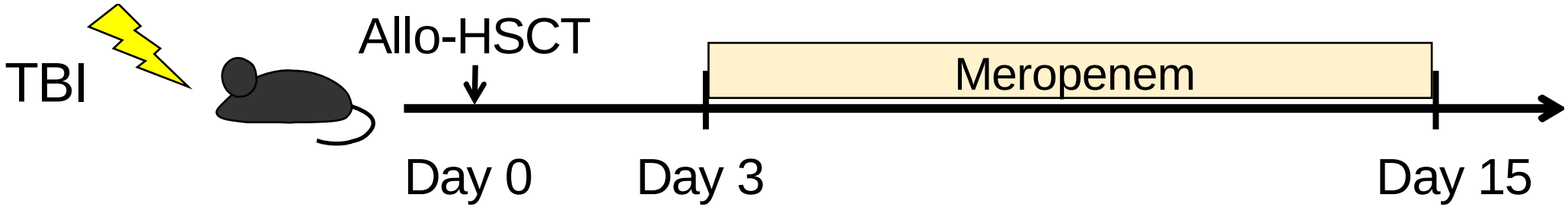
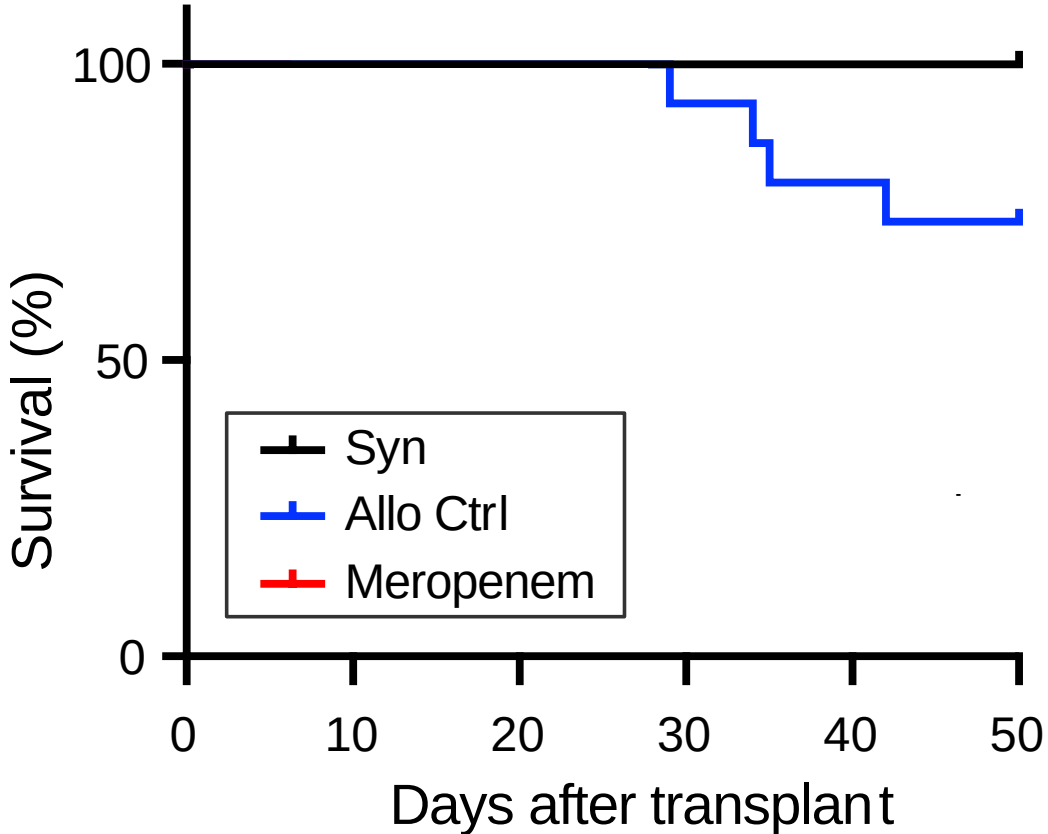


# Meropenem treatment is associated with aggravated intestinal GVHD



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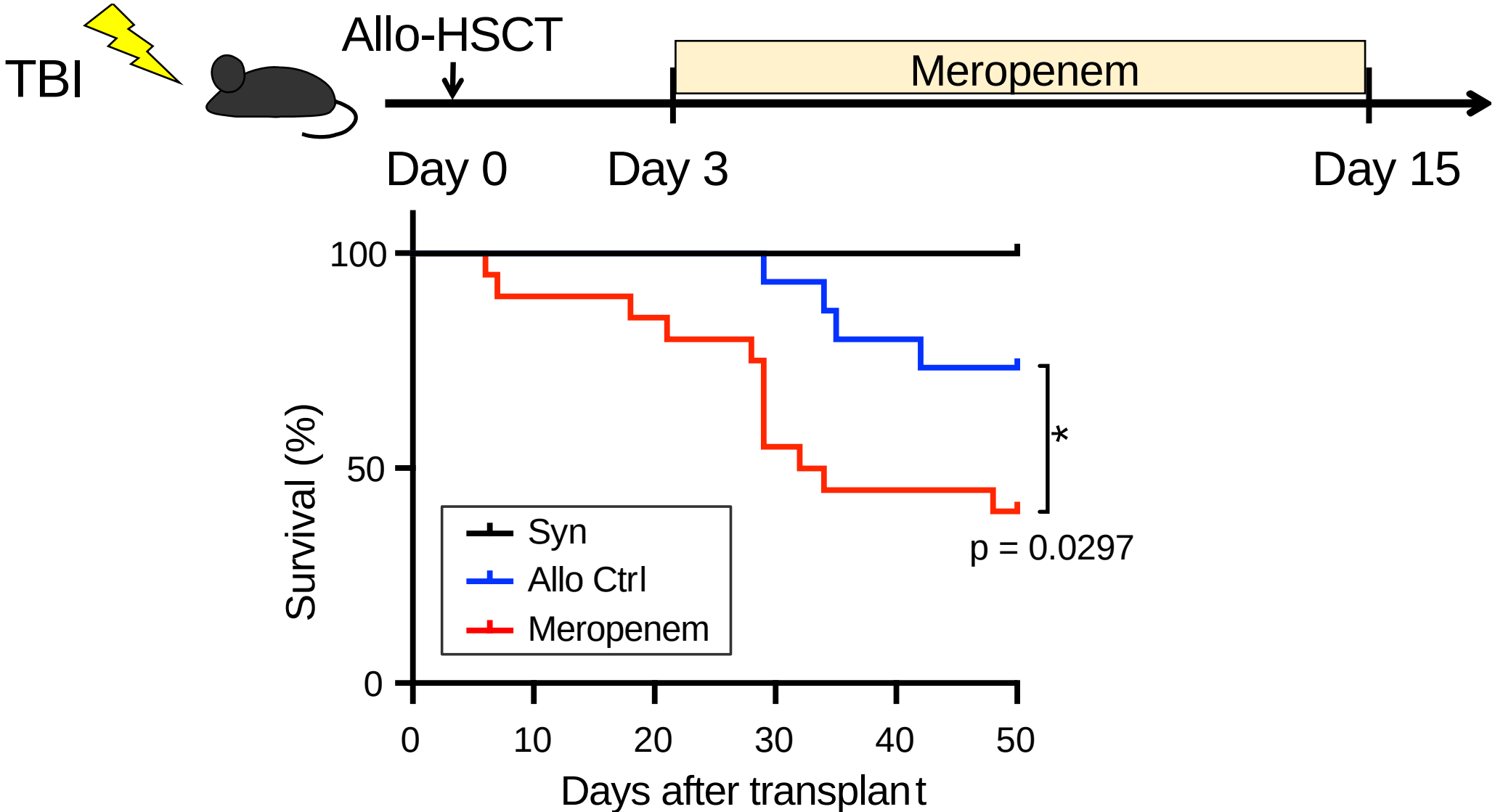
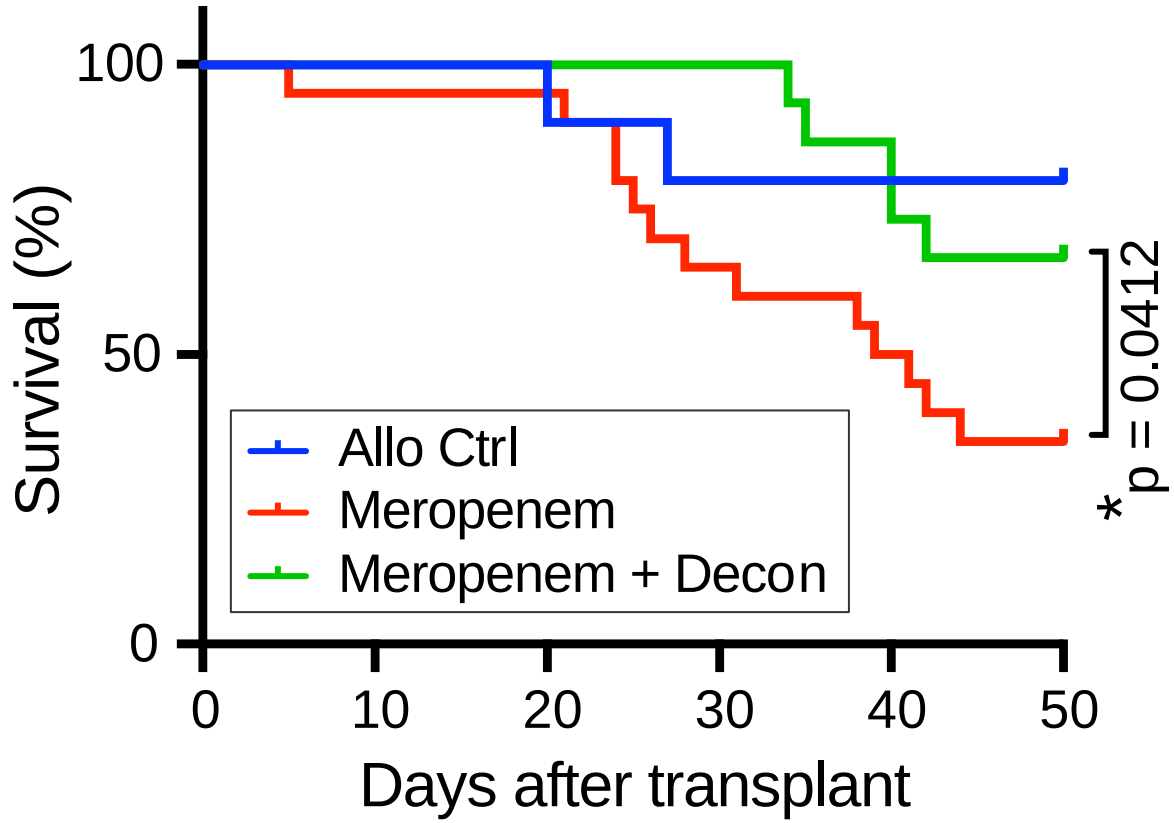
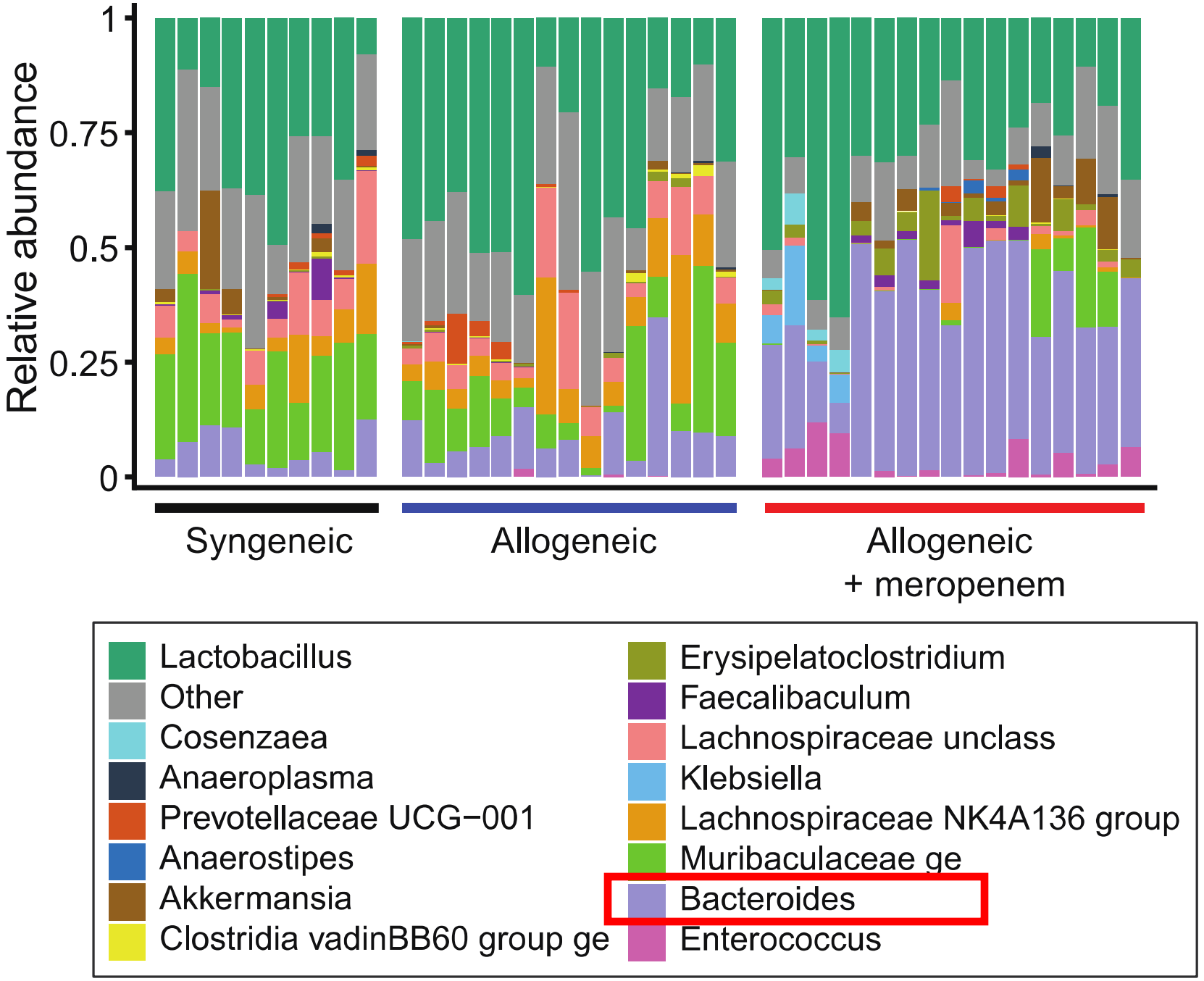


# Decontamination Can Rescue Meropenem-Treated GVHD mice

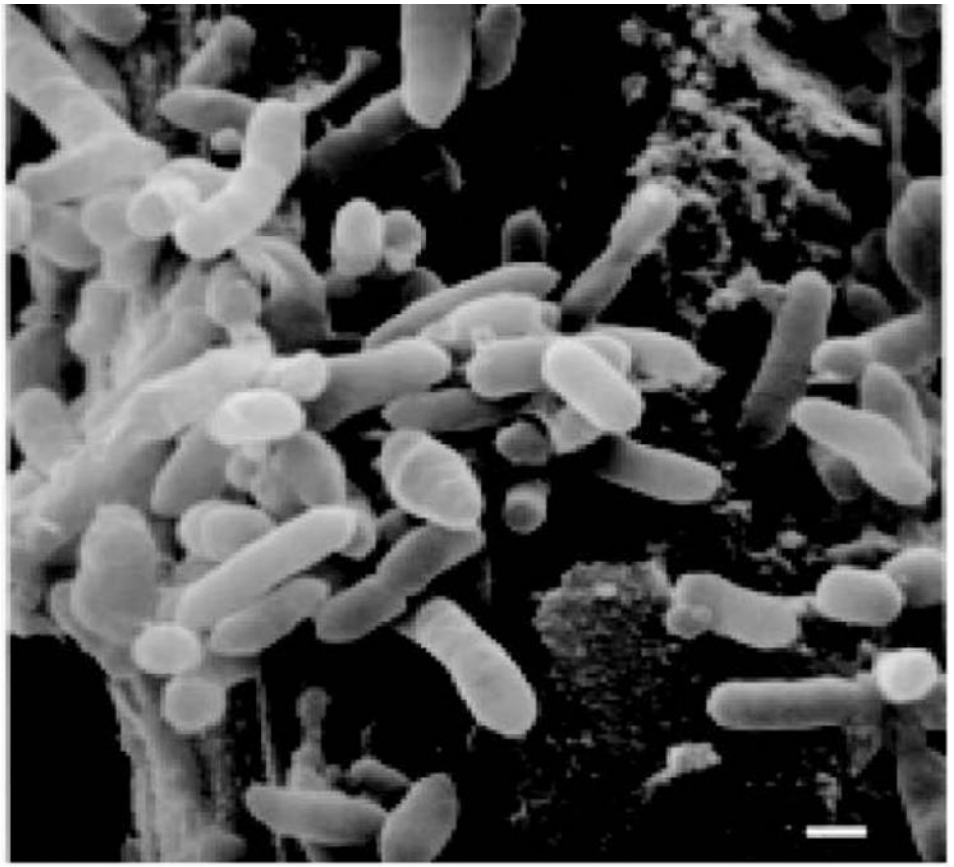


*Bacteroides* is increased in meropenem-treated GVHD mice



# *Bacteroides thetaiotaomicron*

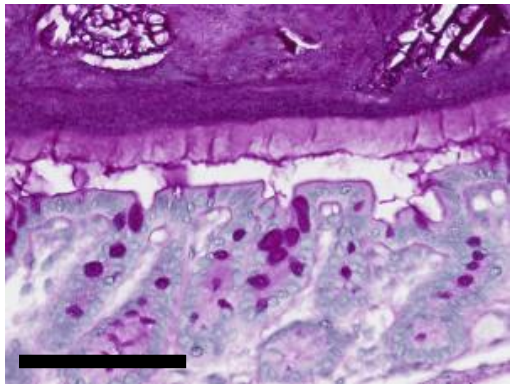
- An intestinal bacterial found in both mice and humans
- Has a broad ability to digest dietary fibers and intestinal mucus



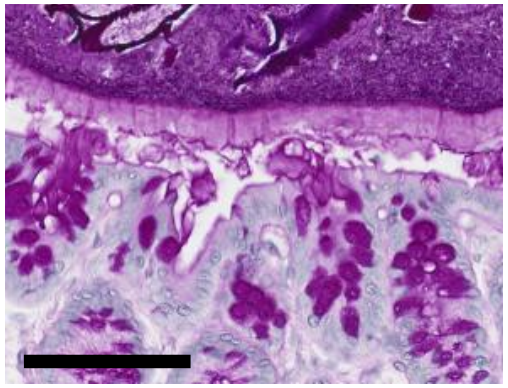
*TerAvest MA et al; Biotechnol Bioeng, 2014*

# Meropenem Arm Showed Thinned Mucus Layer Decontamination Suppressed Mucus Degradation

Syn



Allo Ctrl



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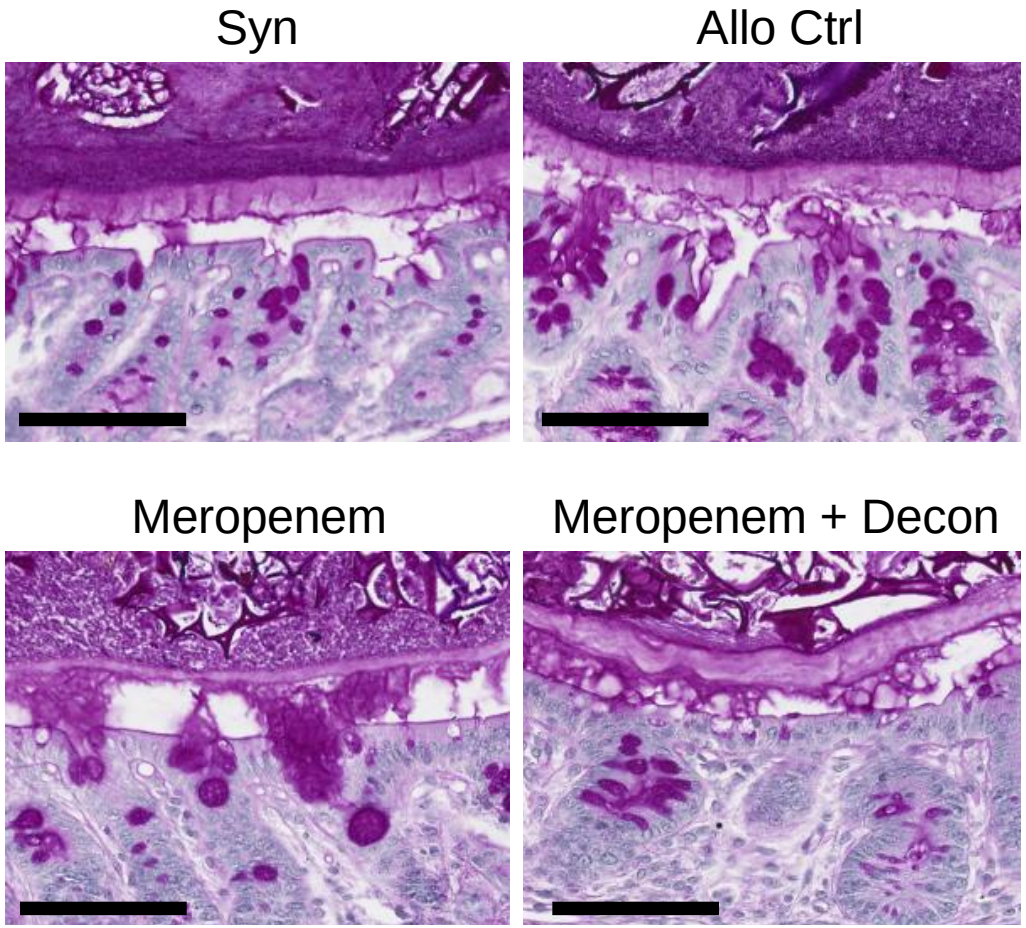
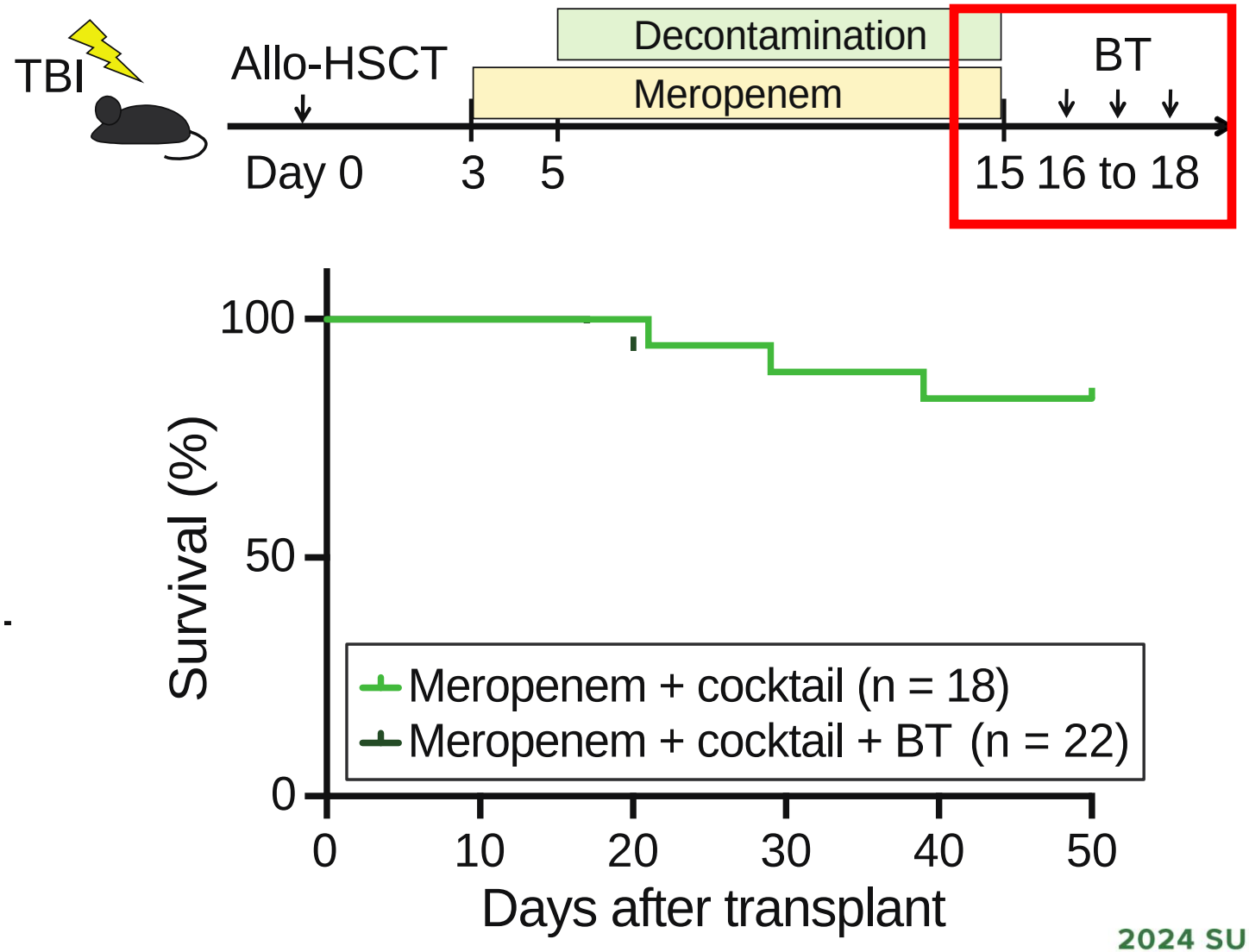


# *B. thetaiotaomicron* Reintroduction Aggravates GVHD in Decontaminated Mice



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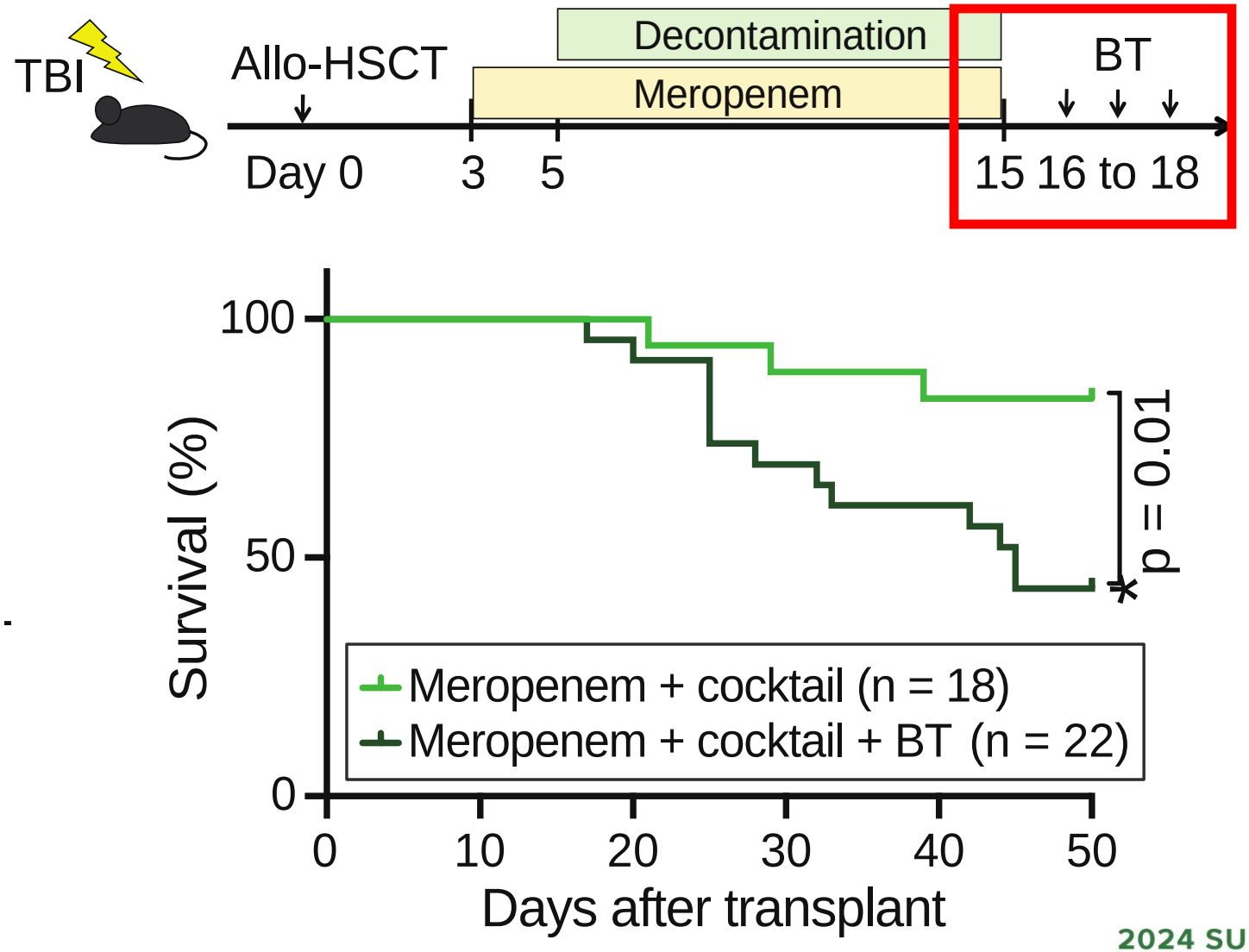
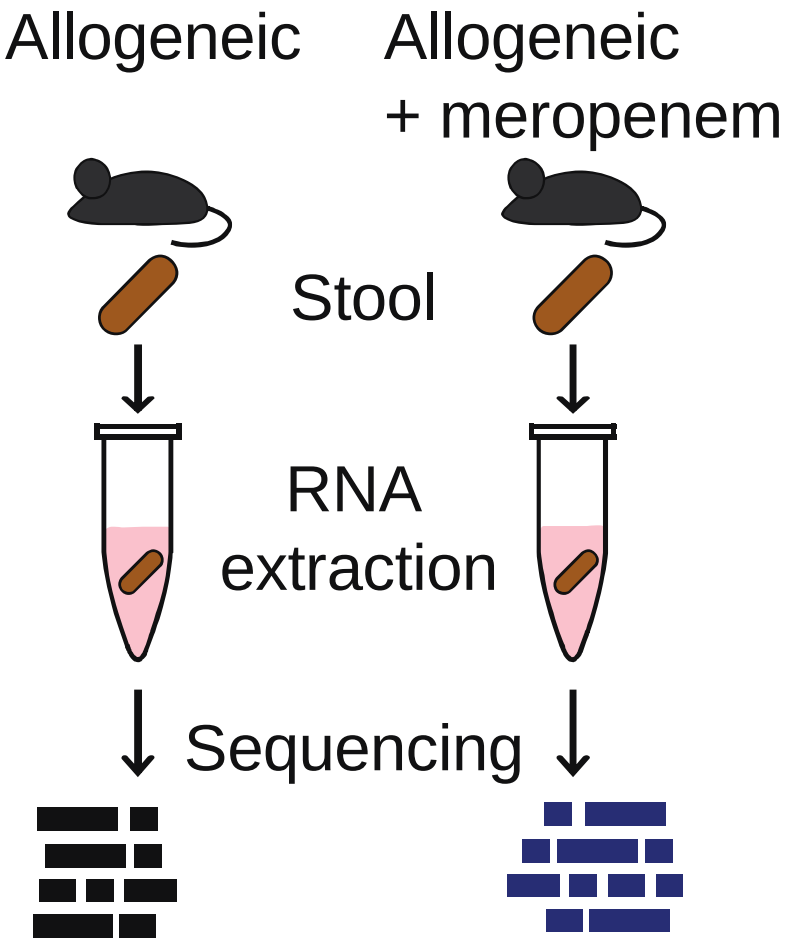


# Meropenem Upregulated the Expression of Mucus-Degrading Enzyme in *B. Thetaiotaomicron*



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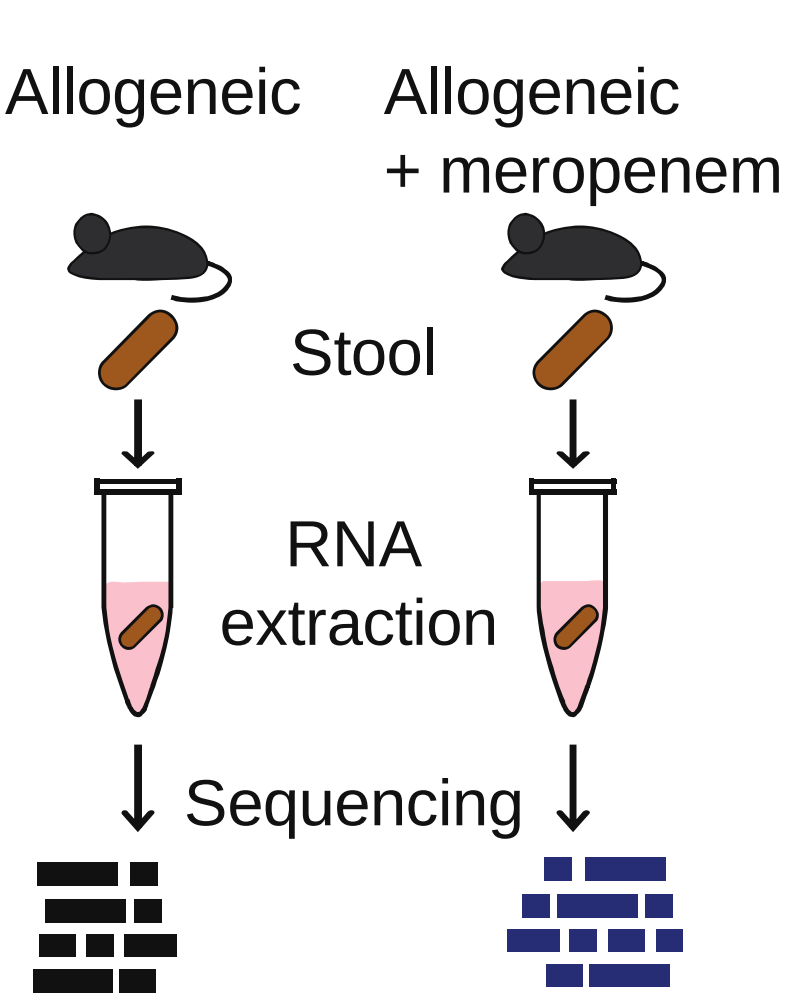


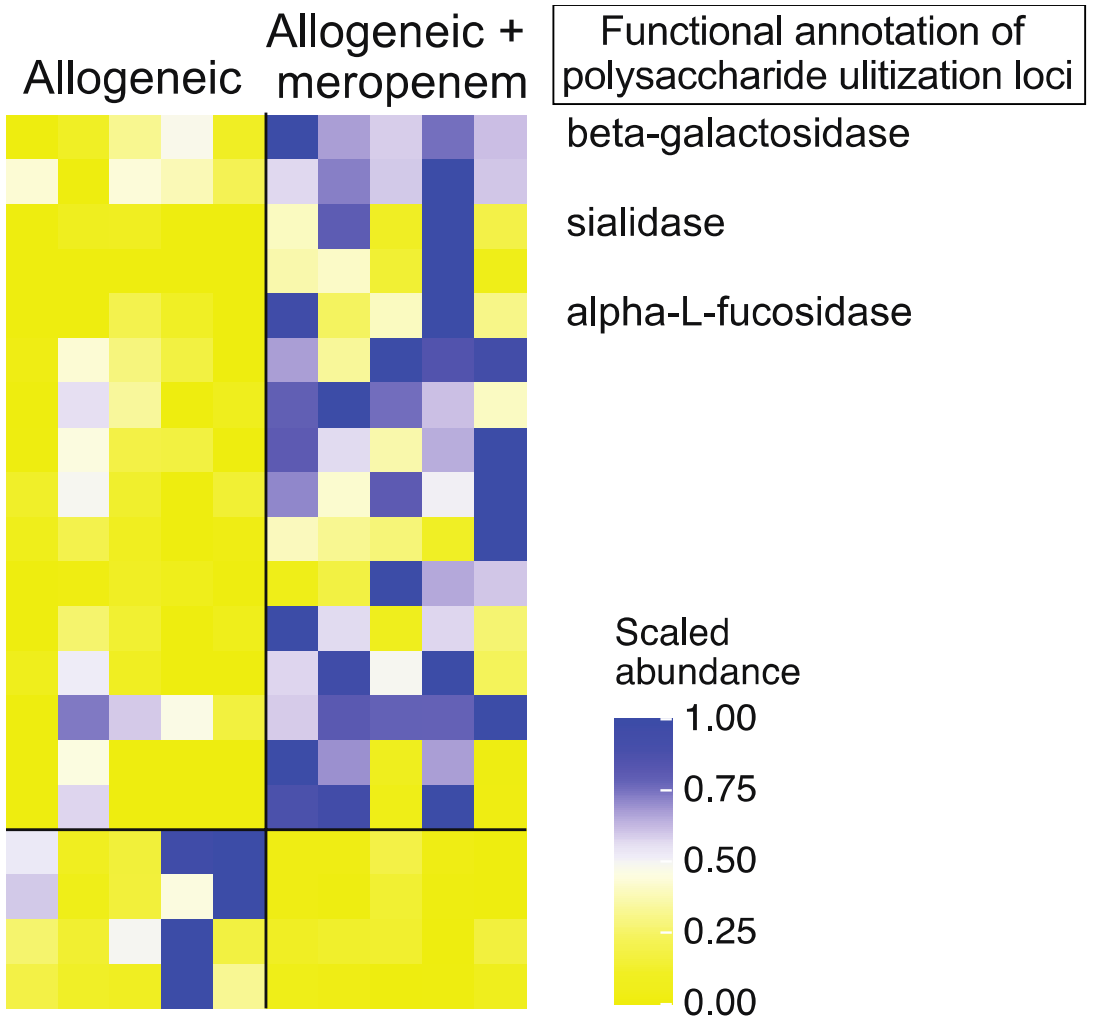

Next question:

Does the microbiota impact GVHD response to treatment with corticosteroids?

# Evaluated Patients Presenting with New Lower GI GVHD (n=37)

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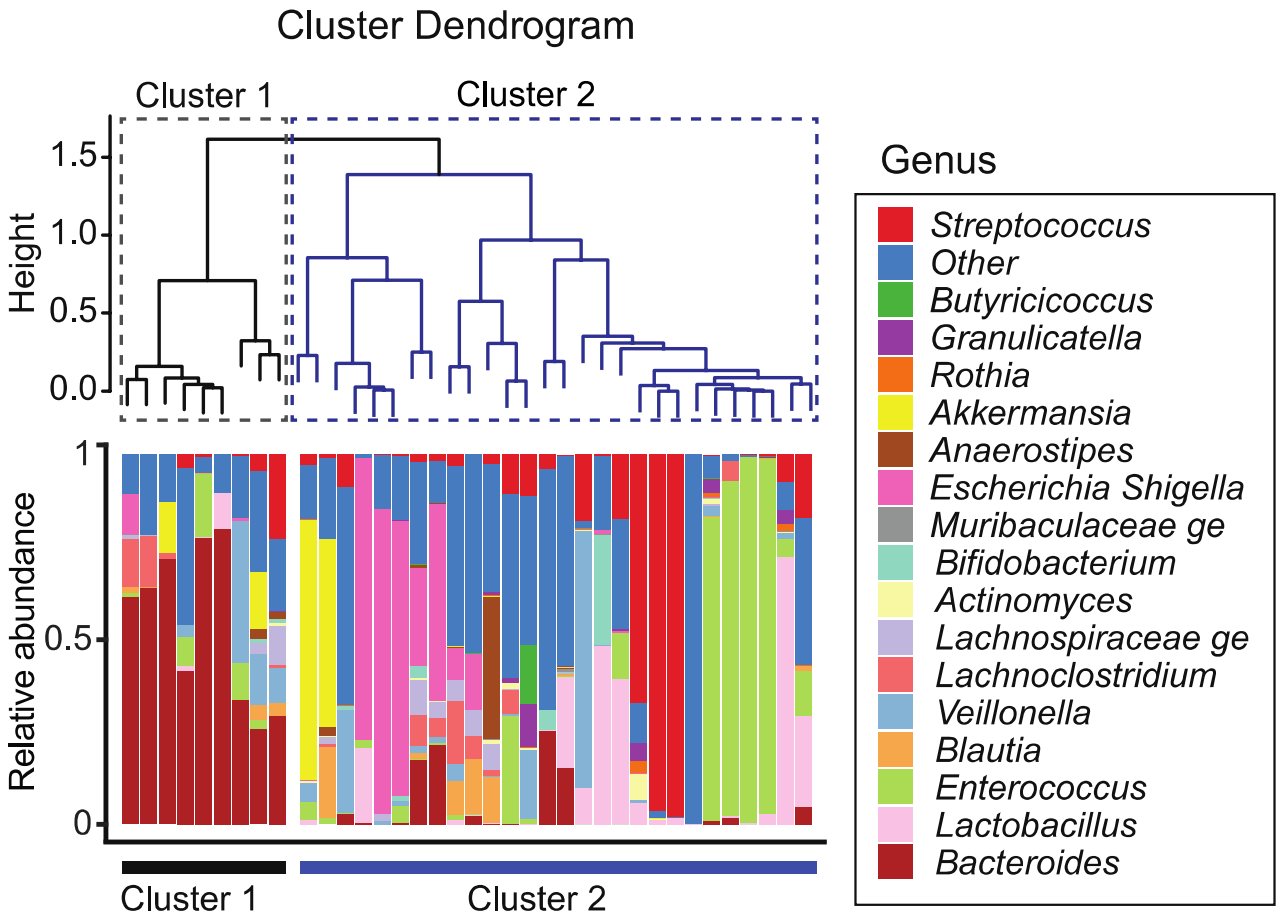
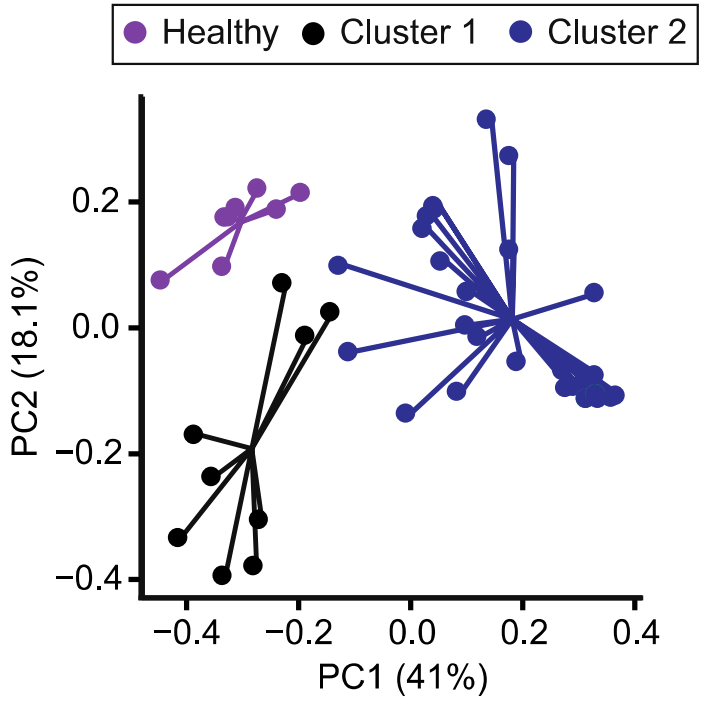
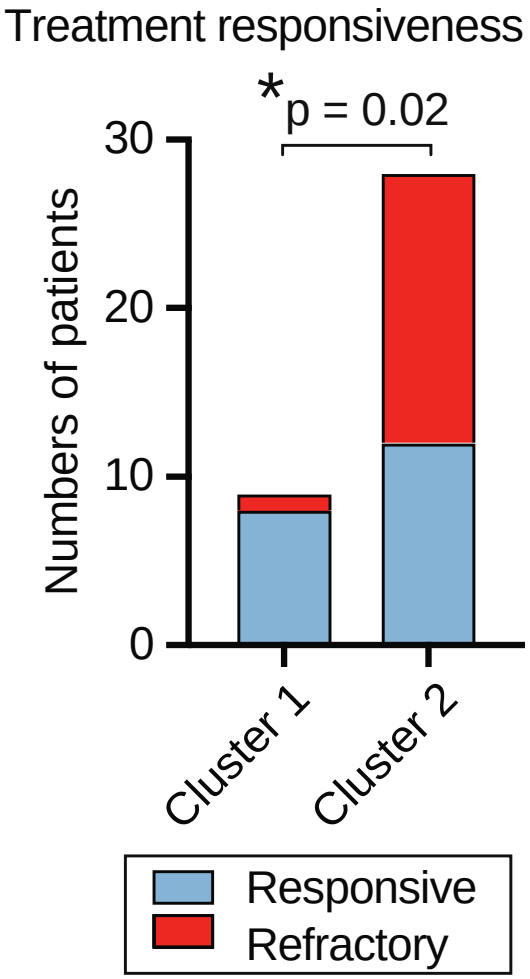
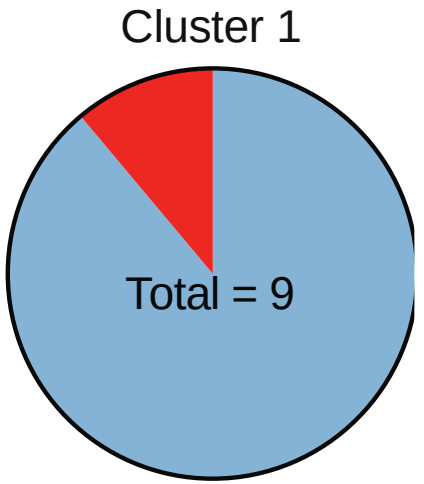
# Patient Microbiome at GVHD Onset

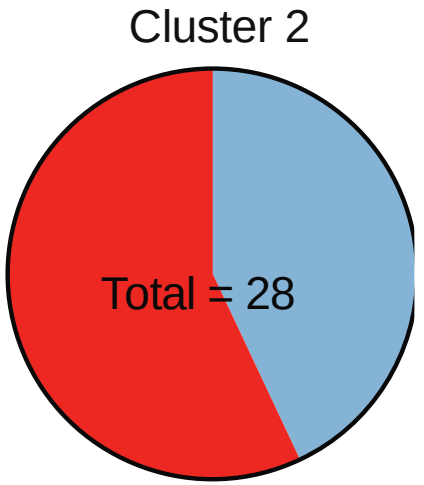


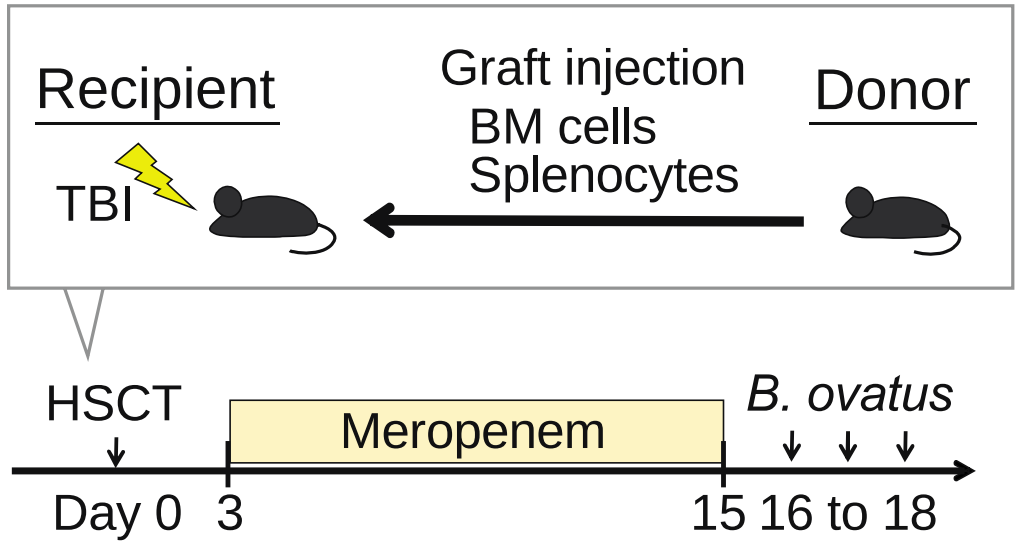
# Cluster 1 was Enriched in GVHD Treatment Responders

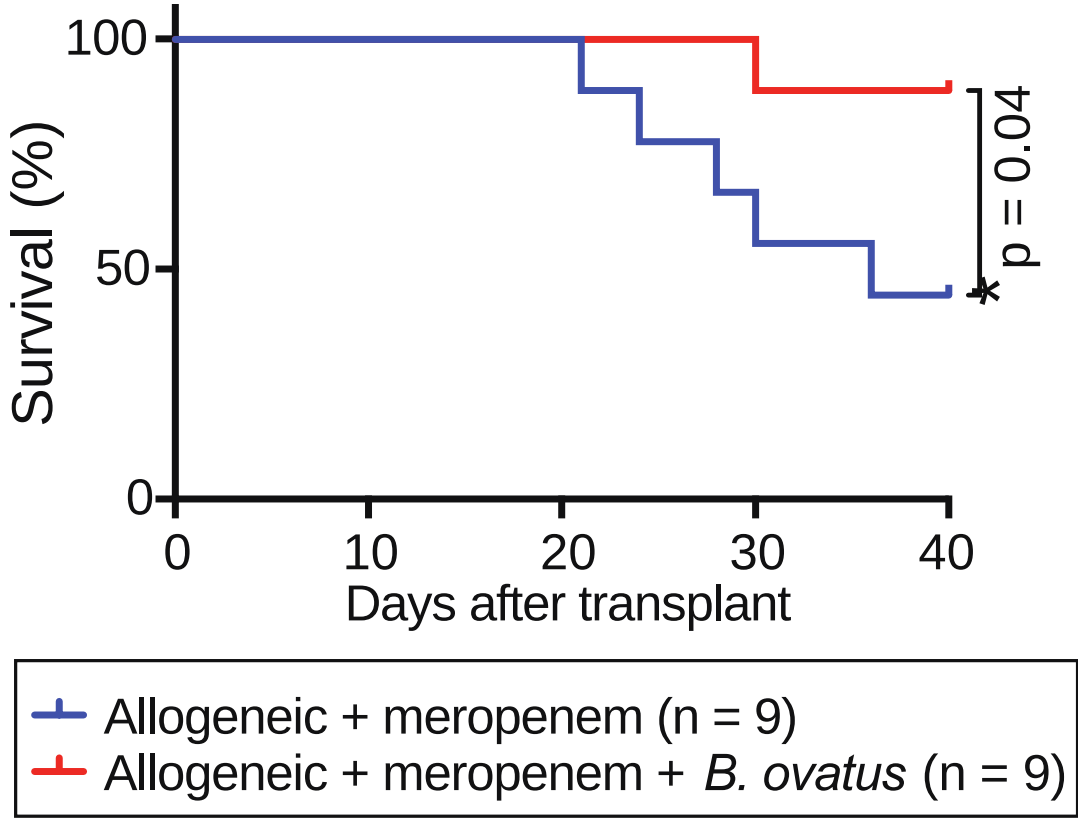


# Introduction of *B. Ovatus* Improved Survival in Meropenem-Induced GVHD Model

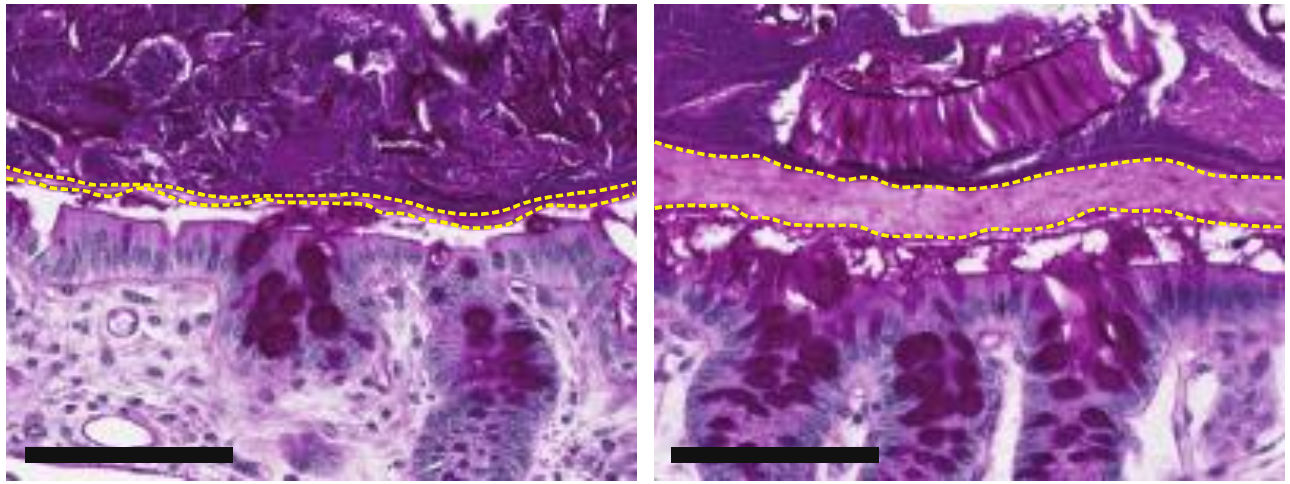


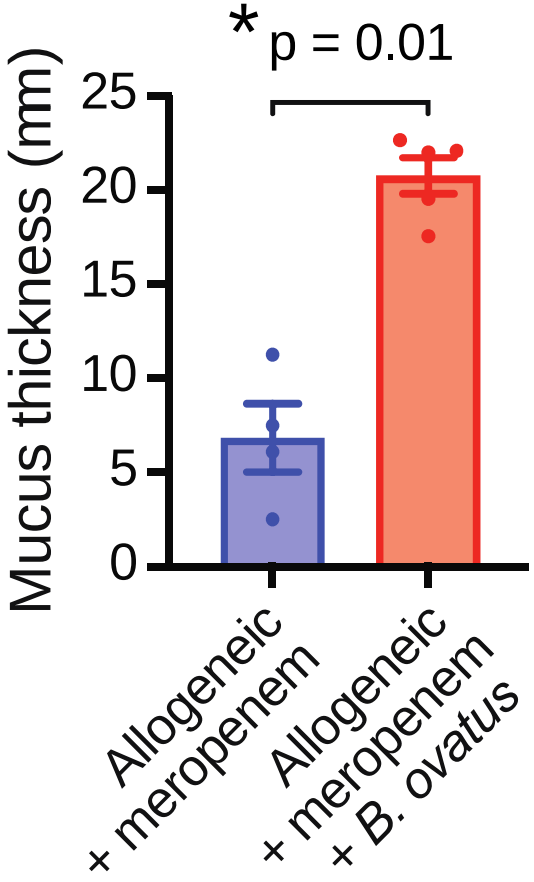



# Introduction of *B. Ovatus* Improved Survival in Meropenem-Induced GVHD Model

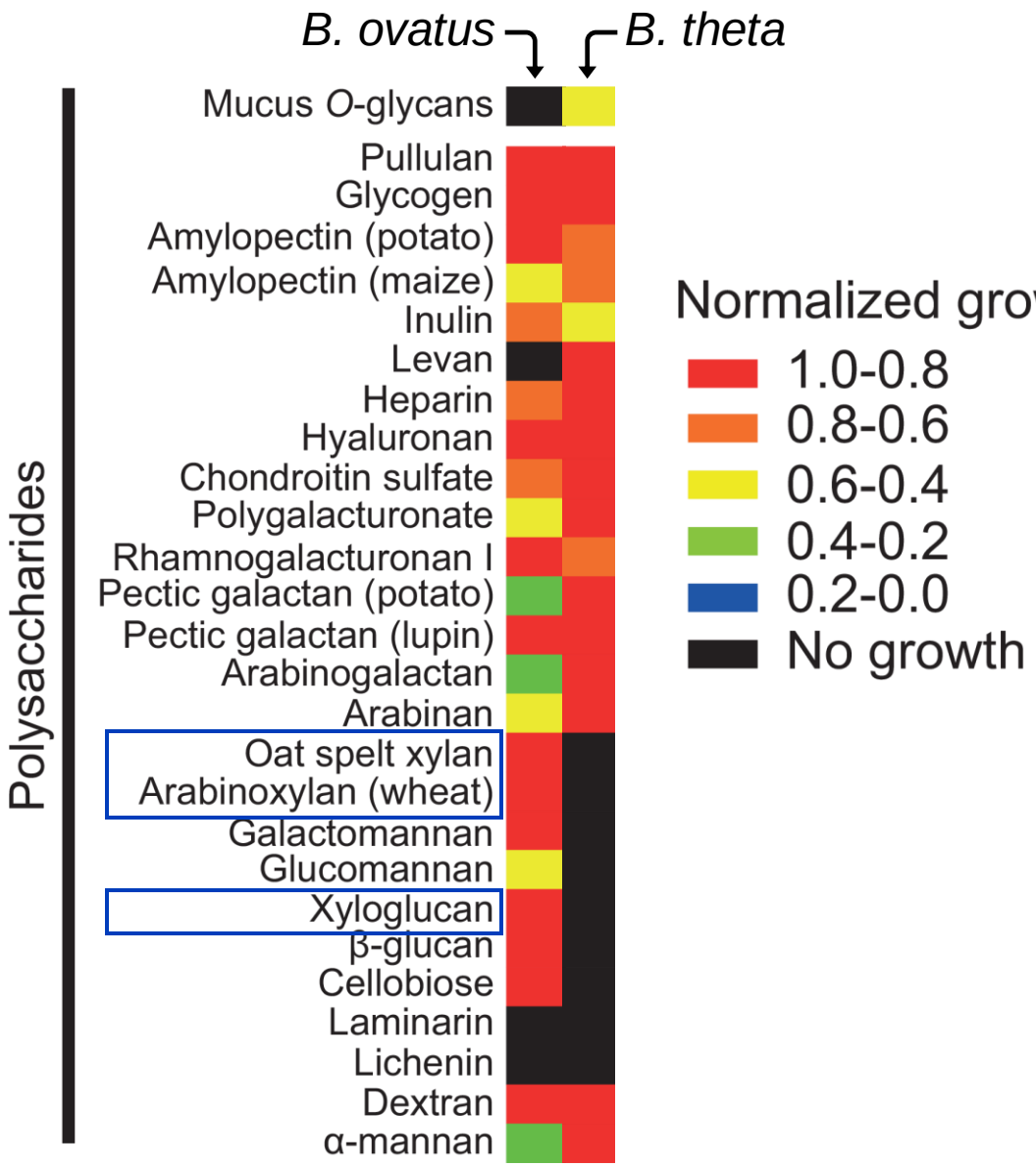
Allogeneic + meropenem

Allogeneic + meropenem + *B. ovatus*



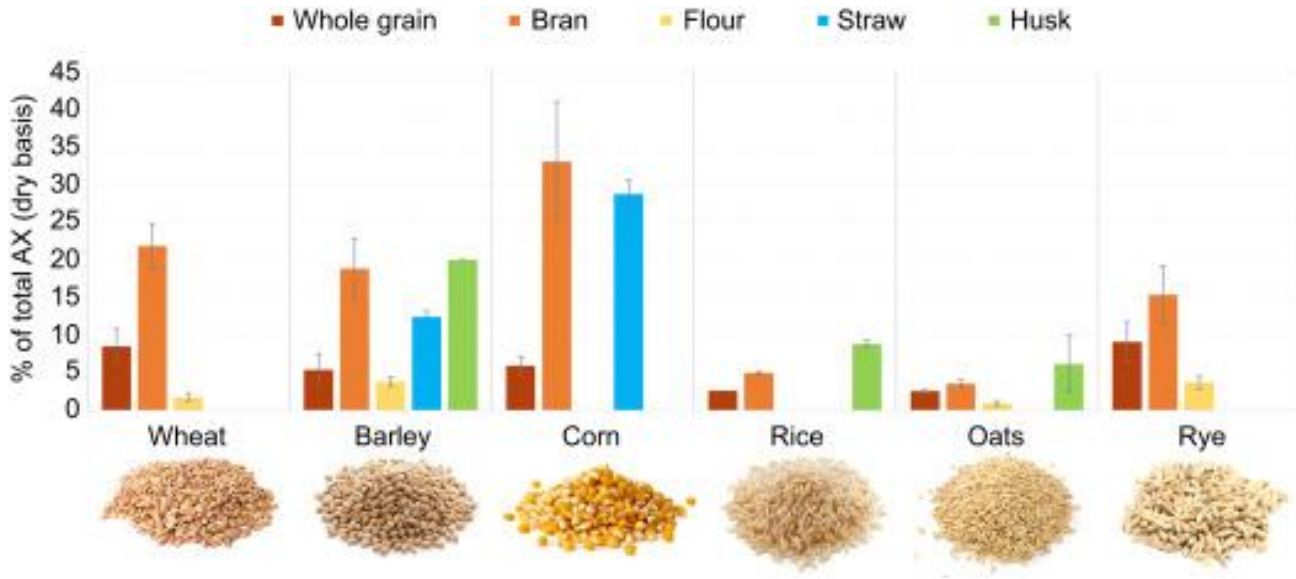


# *B. ovatus* and *B. theta* – A Tale of Two *Bacteroides*



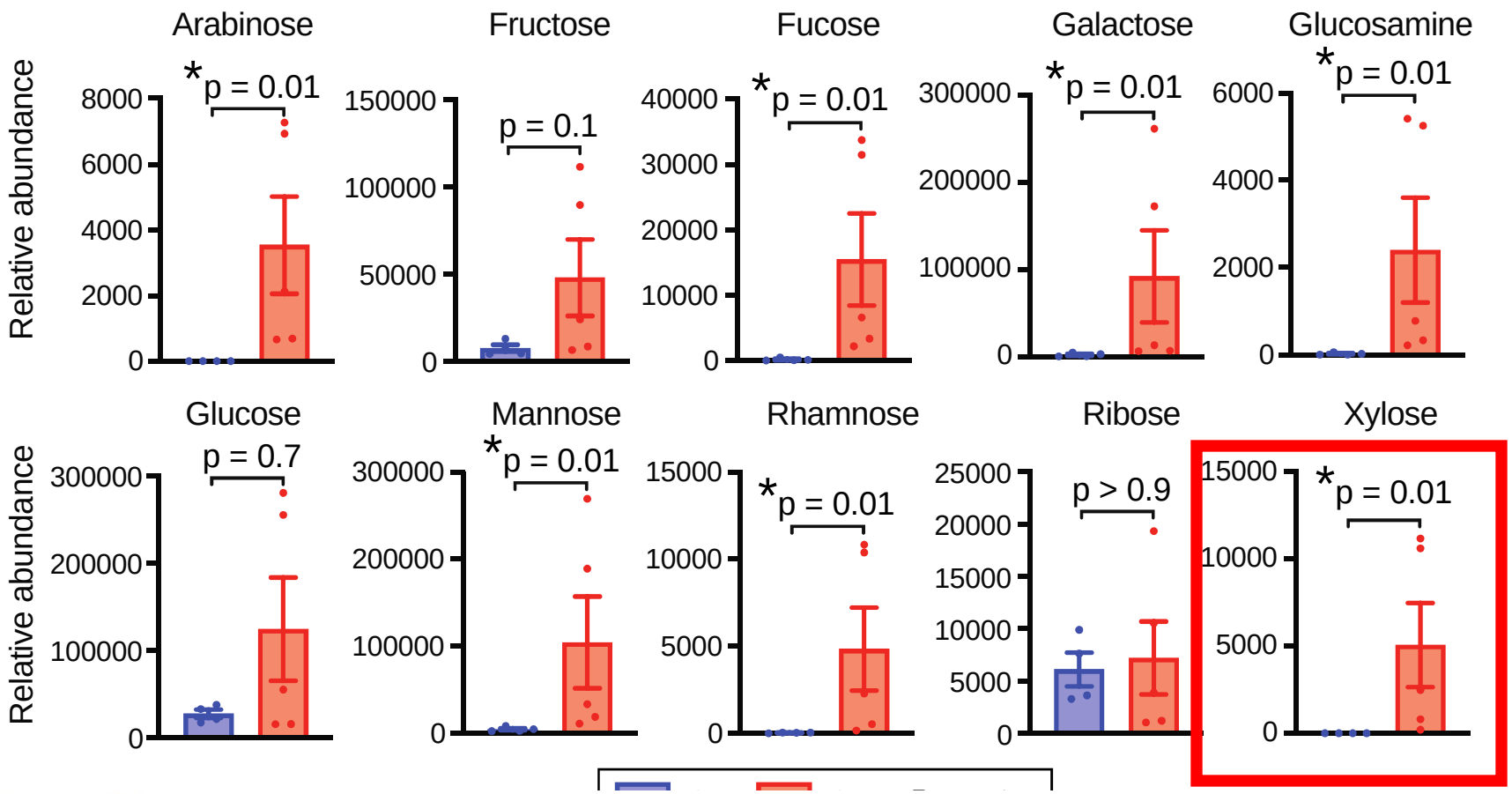

Normalized growth:

- 1.0-0.8
- 0.8-0.6
- 0.6-0.4
- 0.4-0.2
- 0.2-0.0
- No growth

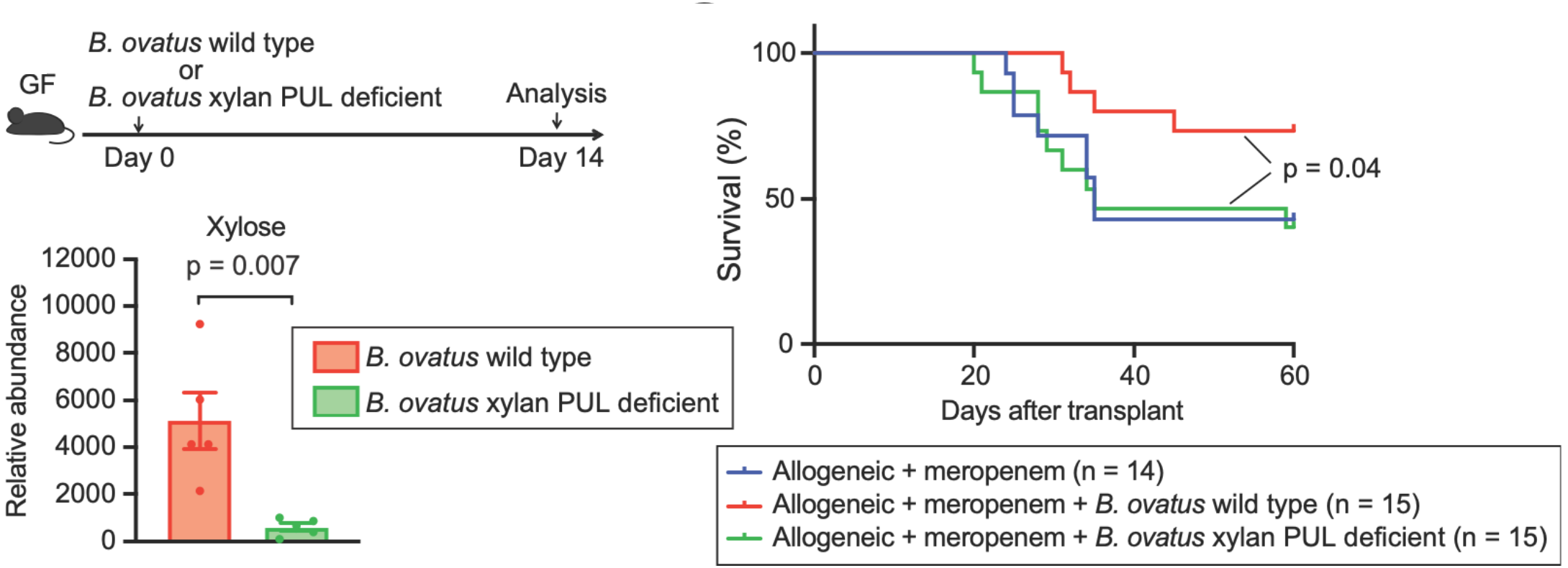



*Cell-2016-Desai MS, et al*
*Sustainable Recovery and Reutilization of Cereal Processing By-Products 2018 - Bastos R, et al*

# *B. ovatus* Introduction Increases Intestinal Sugar Concentrations

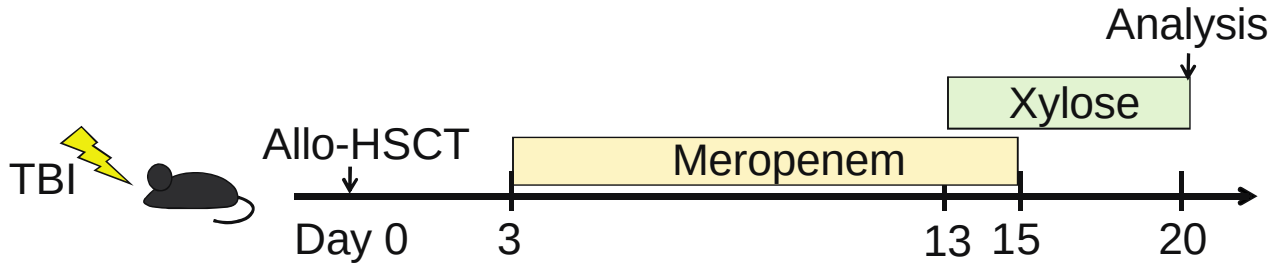


# An engineered mutant version of *B. ovatus* (xylanase insufficient) fails to rescue mice with GVHD after meropenem

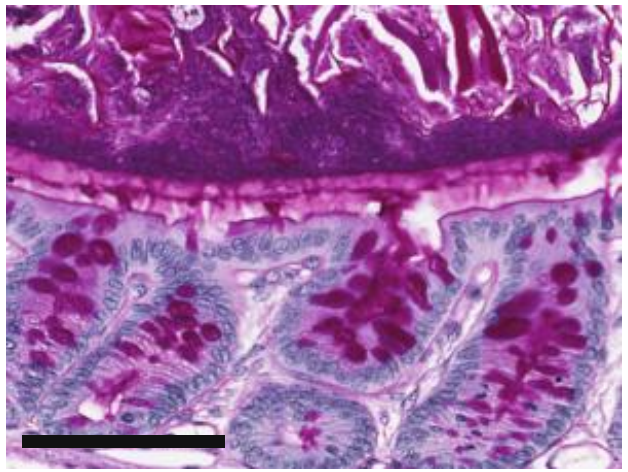



*courtesy of Eric Martens, U. Michigan*

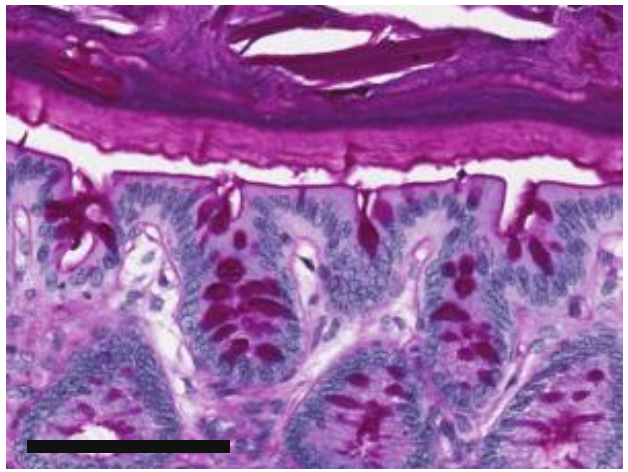
# Supplementation of Xylose Resulted in a Significantly Thicker Mucus Layer



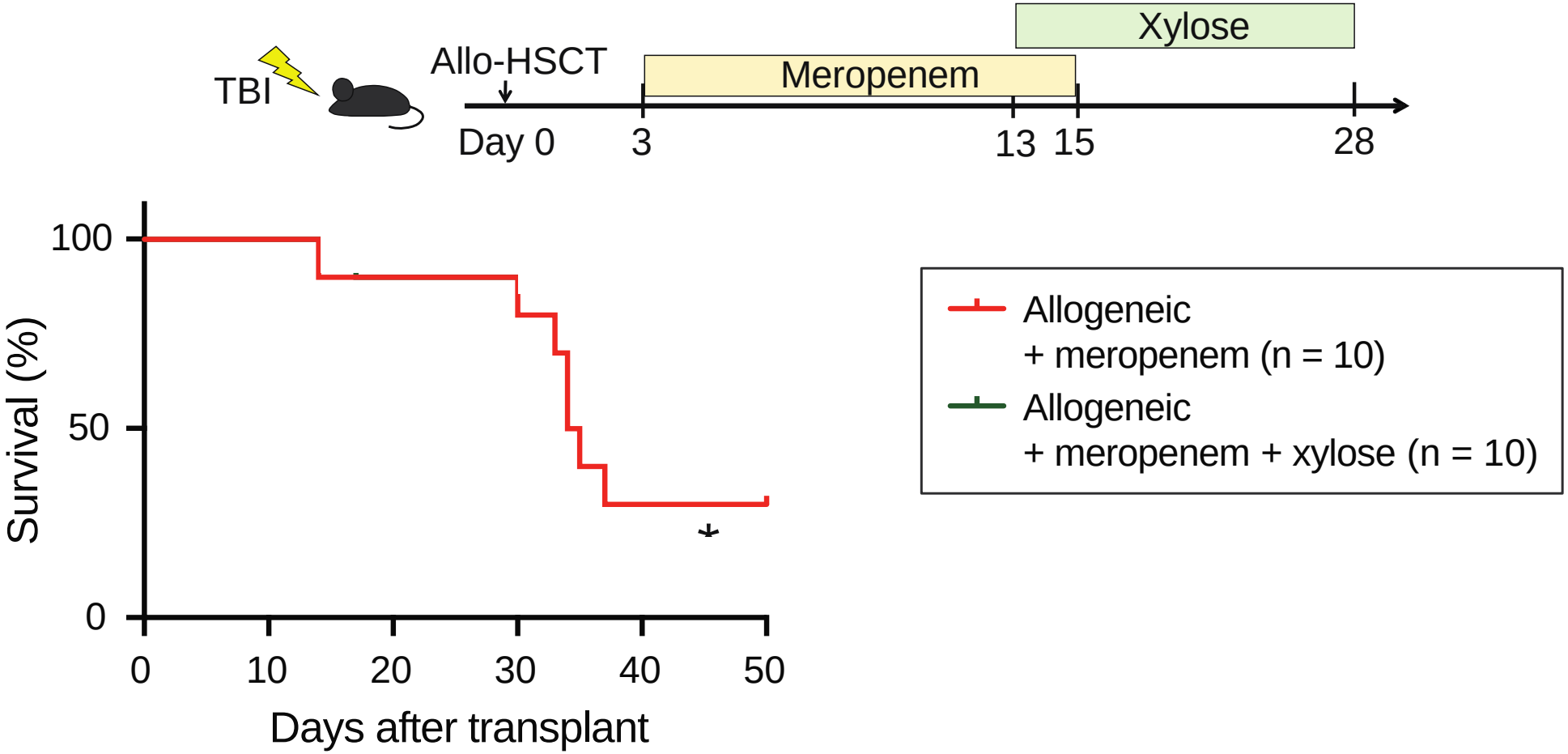

Allogeneic + meropenem



Allogeneic + meropenem + xylose



# Supplementation of Xylose Improved Survival in Meropenem-Treated Mice



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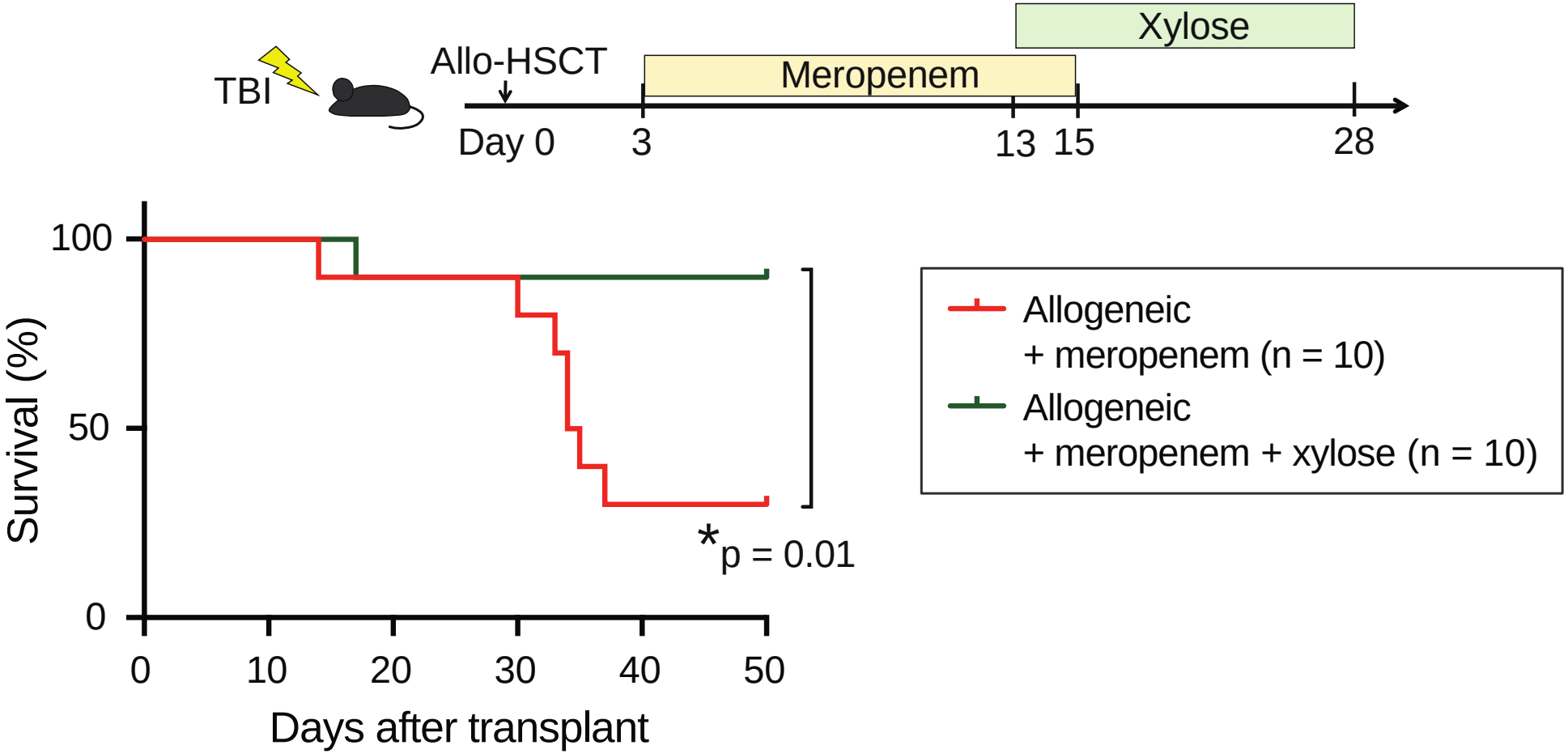
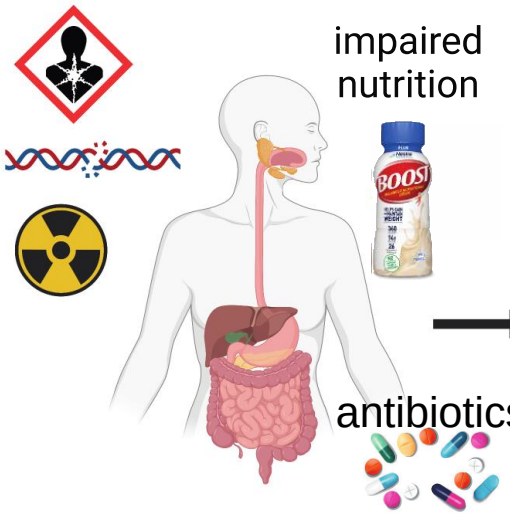
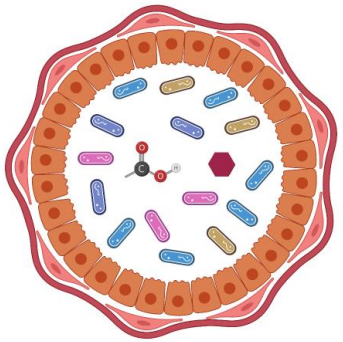
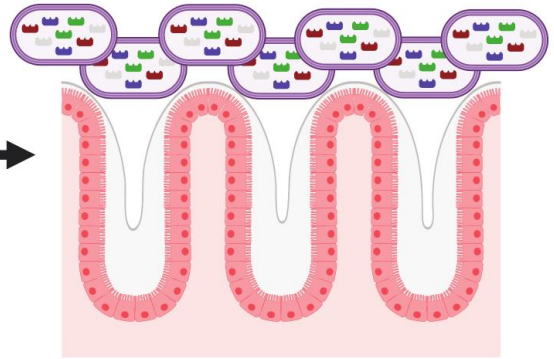


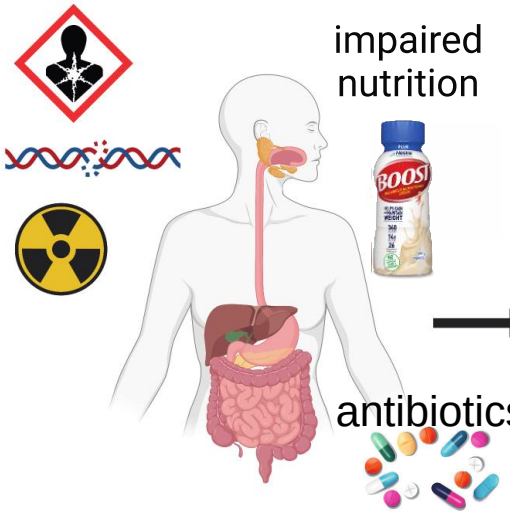



low luminal
metabolite levels

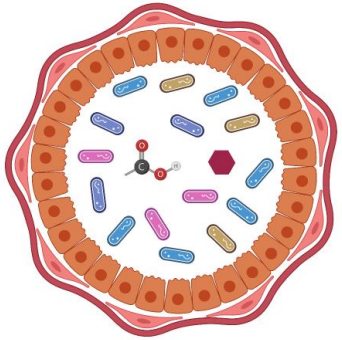


- high mucus degrader abundance
- high expression of mucolytic enzymes
- compromised colonic mucus barrier
- inflamed epithelium

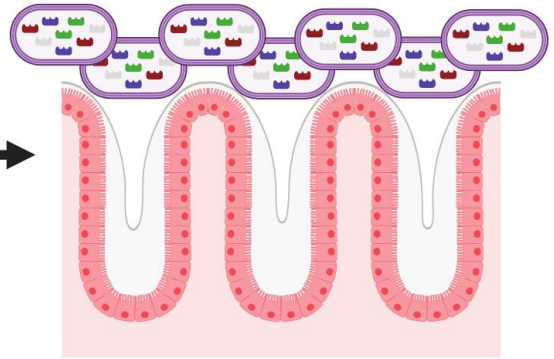


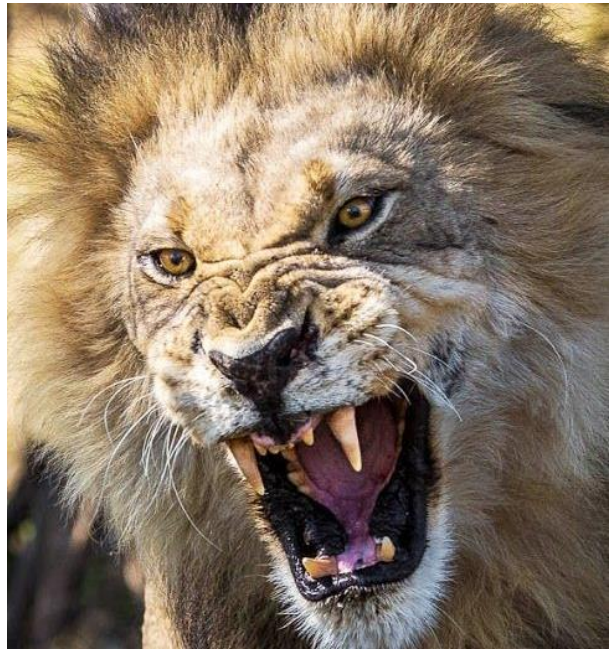


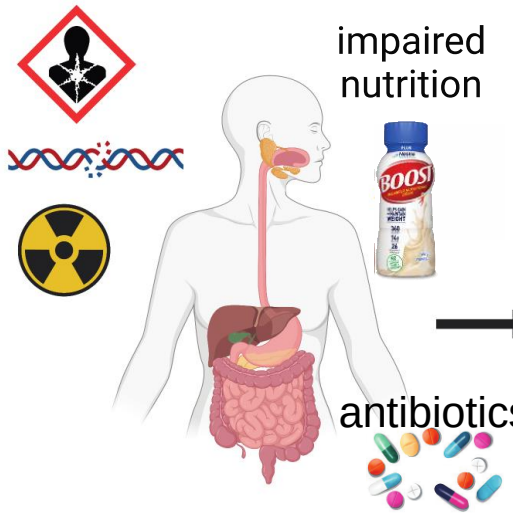

low luminal
metabolite levels



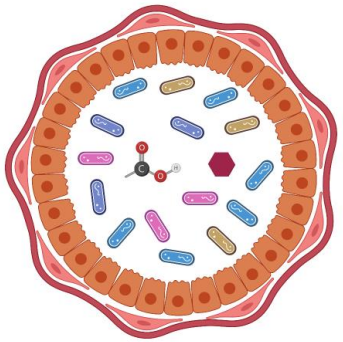
- high mucus degrader abundance
- high expression of mucolytic enzymes
- compromised colonic mucus barrier
- inflamed epithelium



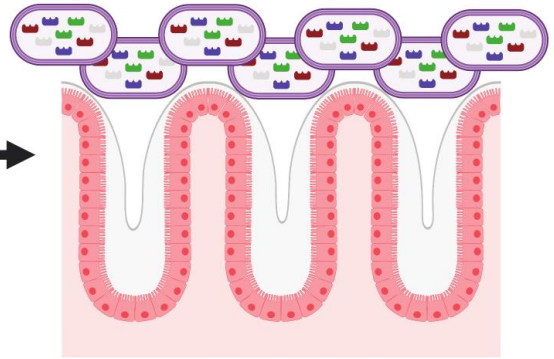


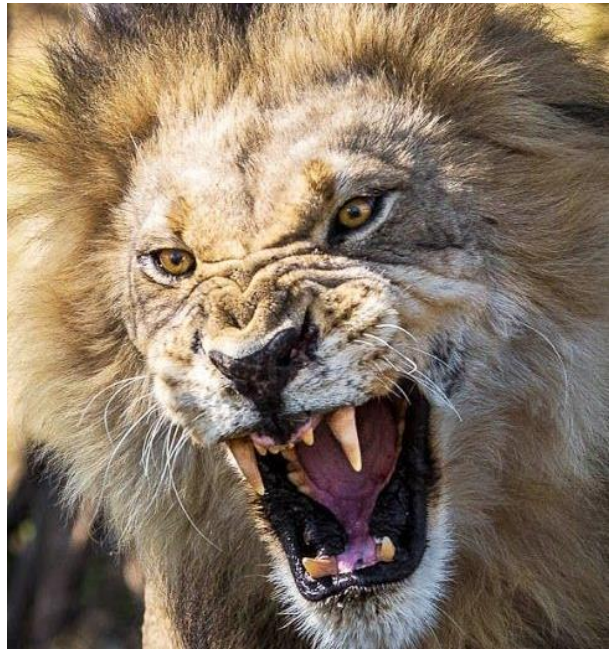


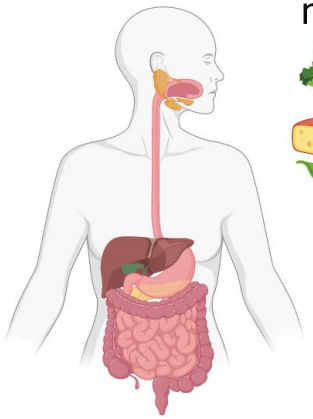

low luminal
metabolite levels



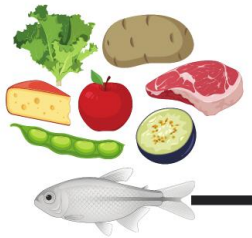
- high mucus degrader abundance
- high expression of mucolytic enzymes
- compromised colonic mucus barrier
- inflamed epithelium



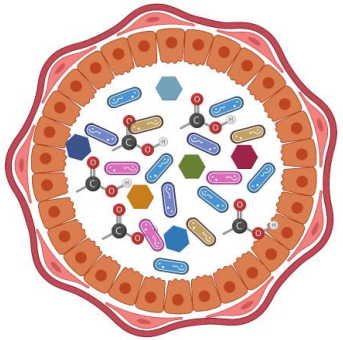




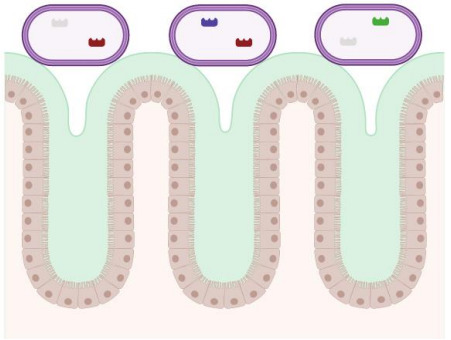
normal
nutrition



high luminal
metabolite levels



- low mucus degrader abundance
- low expression of mucolytic enzymes
- intact colonic mucus barrier
- healthy epithelium

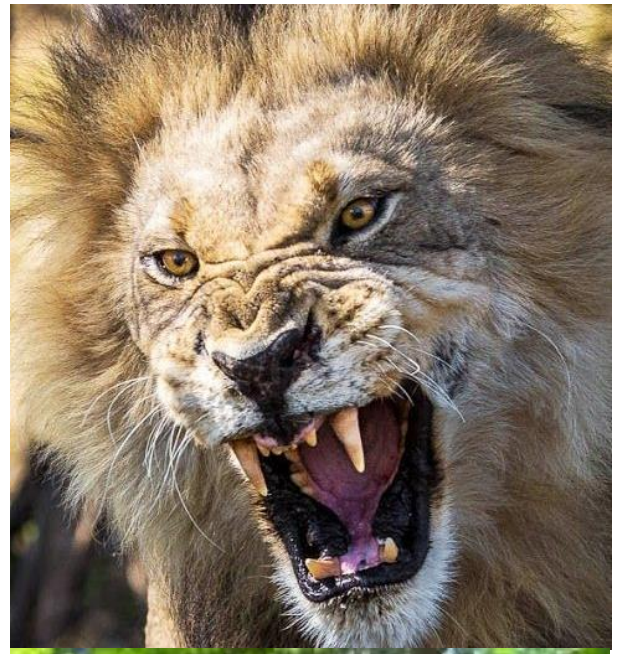


impaired nutrition

antibiotics

low luminal metabolite levels

- high mucus degrader abundance
- high expression of mucolytic enzymes
- compromised colonic mucus barrier
- inflamed epithelium



normal nutrition

high luminal metabolite levels

- low mucus degrader abundance
- low expression of mucolytic enzymes
- intact colonic mucus barrier
- healthy epithelium

# Lessons Learned

- Antibiotics are important tools for treating infections but can have side effects, including injuring the microbiome
- Diet and nutrition are important for supporting the microbiome, especially consuming a variety of different fruits and vegetables on a regular basis
- Probiotics that are currently available in pharmacies and health food stores are probably not beneficial in restoring the microbiome – they don't include the right beneficial bacteria
- Potentially more effective strategies are in clinical trials, including fecal transplantation and mixtures of cultured bacteria

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# Acknowledgements


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# Questions?

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