# Gut Bugs Trial
## Faecal microbiome transfer for the treatment of adolescent obesity – RCT


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# Acknowledgements


**Study participants and their families**


**Gut Bugs Trial Team**

- **Dr Brooke Wilson**
- Dr Karen Leong
- Dr Thilini Jayasinghe
- Dr Tommi Vatanen
- Dr José Derraik
- Dr Ben Albert
- Dr Yannan Jiang
- Ms Wendy Ranson
- Dr Valentina Chiavaroli
- A. Prof Darren Svirskis
- A. Prof Kathryn Beck
- A. Prof Cathryn Conlon
- Dr William Schierding
- Dr David Holland
- Prof Justin O'Sullivan
- Prof Wayne Cutfield

**Tim Edney and the Rockfield Trust**

**Eric Thorstensen & his team (lab support)**

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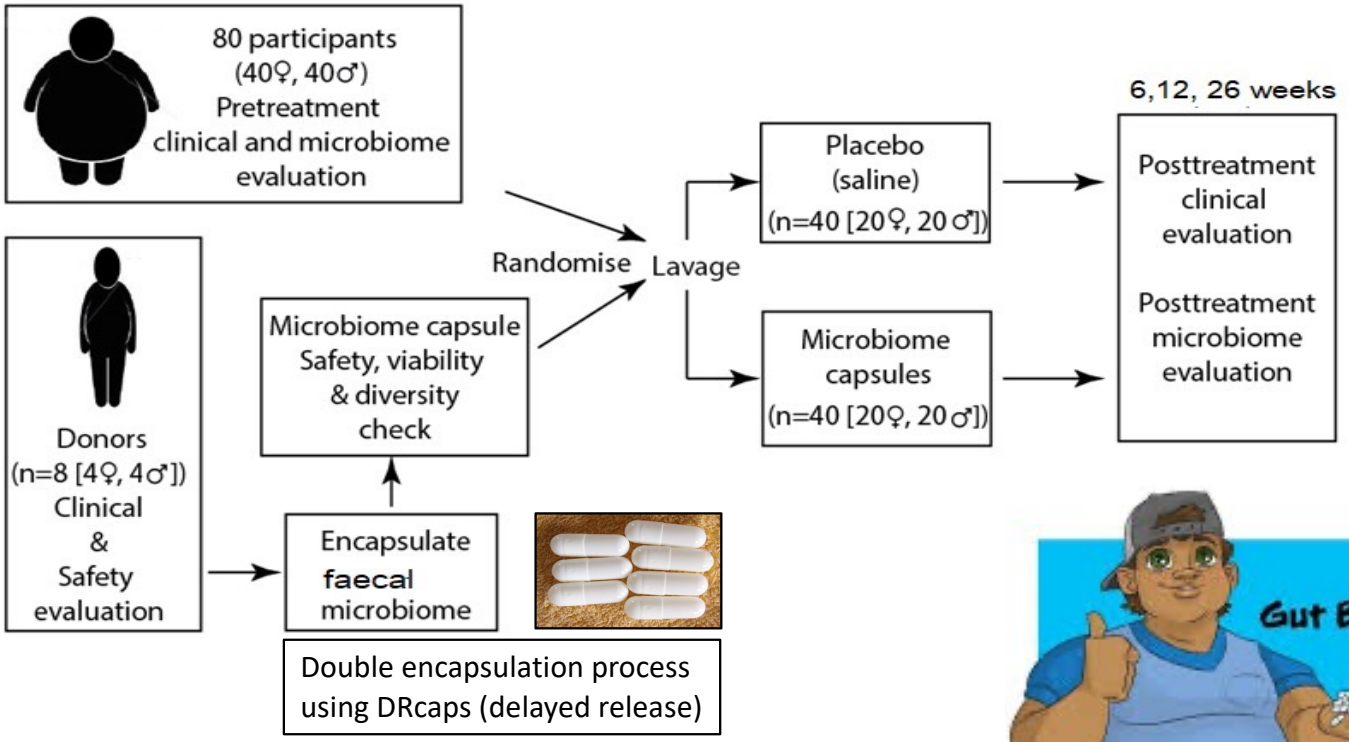
# Hypothesis

FMT in adolescents with obesity would lead to:

- weight loss
- improved metabolism

  (↓ metabolic syndrome & ↑ insulin sensitivity)

# Gut Bugs Trial





Gut Bugs Trial protocol – Leong et al. BMJ Open 2019; e026174

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# FMT NOT associated with weight loss at 6 weeks

| | | FMT | | Placebo | | | |
|---|---|---|---|---|---|---|---|
| | Visit (weeks) | N | mean ± SD | N | mean ± SD | aMD (95% CI) | p-value |
| **BMI SDS** | **0** | 42 | 3.46 ± 0.91 | 45 | 3.21 ± 0.64 | | |
| | **6** | 39 | 3.50 ± 0.97 | 44 | 3.29 ± 0.66 | -0.03 (-0.07, 0.02) | 0.29 |

BMI SDS is BMI adjusted for age and sex

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# FMT led to reduction in android-to-gynoid fat ratio (A/G ratio)

| | Visit (weeks) | FMT N | FMT mean ± SD | Placebo N | Placebo mean ± SD | aMD (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| **ALL** | | | | | | | |
| **A/G ratio** | **0** | 42 | 1.093 ± 0.116 | 45 | 1.074 ± 0.084 | | |
| | **6** | 39 | 1.081 ± 0.126 | 44 | 1.088 ± 0.101 | -0.021 (-0.041, -0.001) | **0.042** |
| | **12** | 38 | 1.083 ± 0.117 | 41 | 1.095 ± 0.098 | -0.023 (-0.043, -0.003) | **0.028** |
| | **26** | 37 | 1.075 ± 0.119 | 41 | 1.088 ± 0.088 | -0.029 (-0.049, -0.008) | **0.0069** |
| **FEMALES** | | | | | | | |
| **A/G ratio** | **0** | 25 | 1·027 ± 0·088 | 26 | 1·032 ± 0·057 | | |
| | **6** | 24 | 1·013 ± 0·085 | 26 | 1·047 ± 0·074 | -0·029 (-0·053, -0·005) | **0·018** |
| | **12** | 23 | 1·015 ± 0·084 | 23 | 1·054 ± 0·064 | -0·028 (-0·054, -0·003) | **0·027** |
| | **26** | 22 | 1·008 ± 0·084 | 24 | 1·050 ± 0·059 | -0·030 (-0·055, -0·006) | **0·017** |

A/G ratio (abdominal adiposity) was derived from DXA scan

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# FMT associated with resolution of metabolic syndrome

| | Visit | FMT n (%) | Placebo n (%) | aOR (95% CI) | p-value |
|---|---|---|---|---|---|
| **Metabolic syndrome** | **0** | 18 (100%) | 13 (100%) | | |
| | **6** | 13 (81%) | 9 (69%) | 2.00 (0·32, 12.69) | 0·45 |
| | **12** | 5 (38%) | 7 (58%) | 0.42 (0·07, 2·50) | 0·33 |
| | **26** | 4 (27%) | 10 (83%) | 0·06 (0·01, 0.45) | **0·0074** |

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# FMT associated with improvement in insulin sensitivity

| | Visit (weeks) | FMT | | Placebo | | aMD (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| | | N | mean (95% CI) | N | mean (95% CI) | | |
| **HOMA-IR** | **0** | 18 | 8·53 (6.49, 11.22) | 13 | 7·12 (5.18, 9.79) | 1·20 (0·79, 1·82) | 0·38 |
| | **6** | 16 | 6·29 (5.00, 7.92) | 13 | 9·60 (7·41, 12·43) | 0·66 (0·46, 0·93) | **0·018** |
| | **12** | 13 | 8·27 (6·47, 10·58) | 12 | 8·13 (6·23, 10·61) | 1·02 (0·71, 1·46) | 0·93 |
| | 26 | 15 | 7·49 (5·92, 9·48) | 12 | 8·69 (6·66, 11·34) | 0·86 (0·60, 1·23) | 0·41 |

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# So what happened to their gut microbiome?

# One big strain competition experiment

**REVIEW article**

Front. Cell. Infect. Microbiol., 21 January 2019 | https://doi.org/10.3389/fcimb.2019.00002

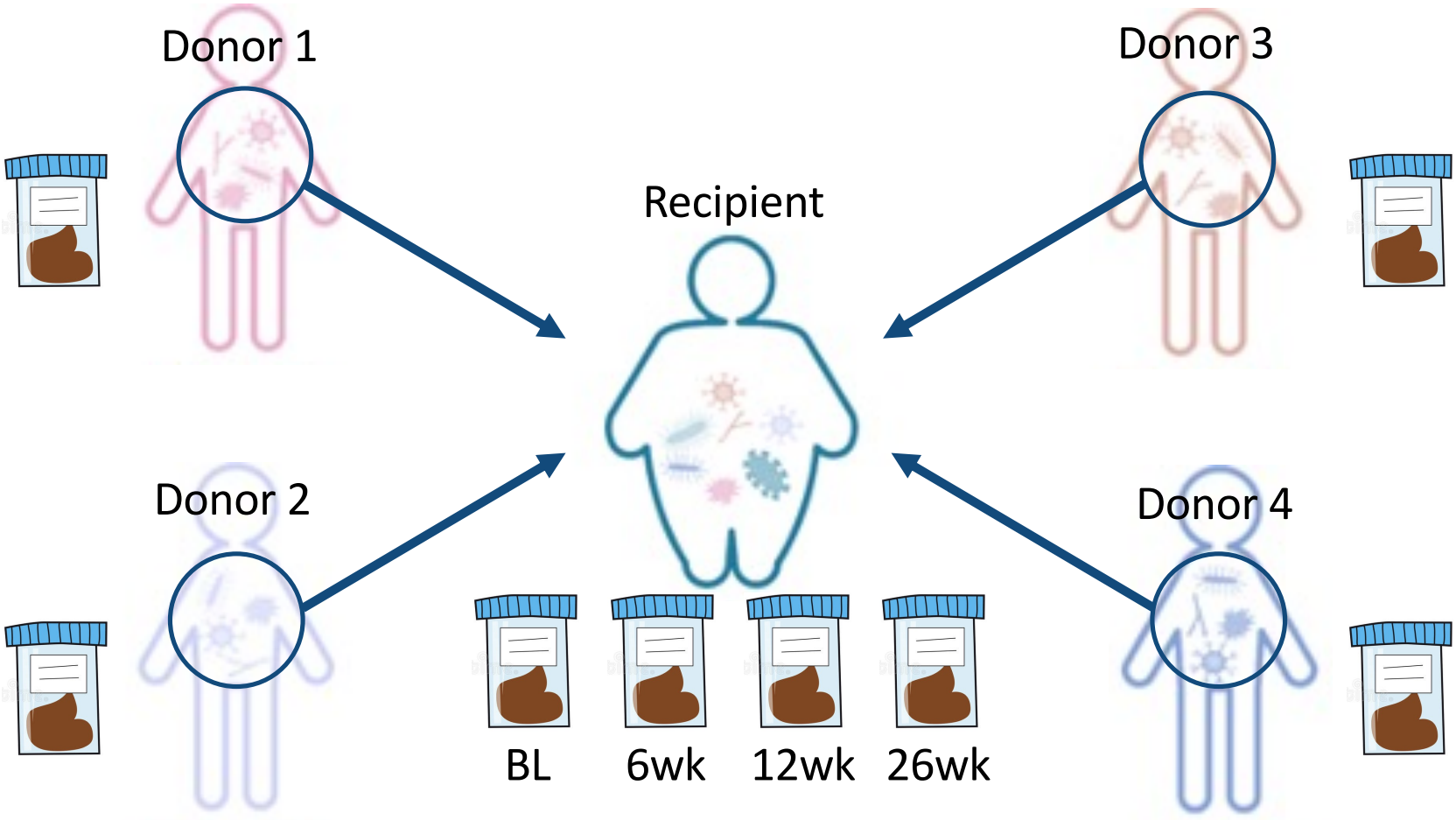
## The Super-Donor Phenomenon in Fecal Microbiota Transplantation


**Brooke C. Wilson**[1], **Tommi Vatanen**[1,2], **Wayne S. Cutfield**[1] and **Justin M. O'Sullivan**[1*]

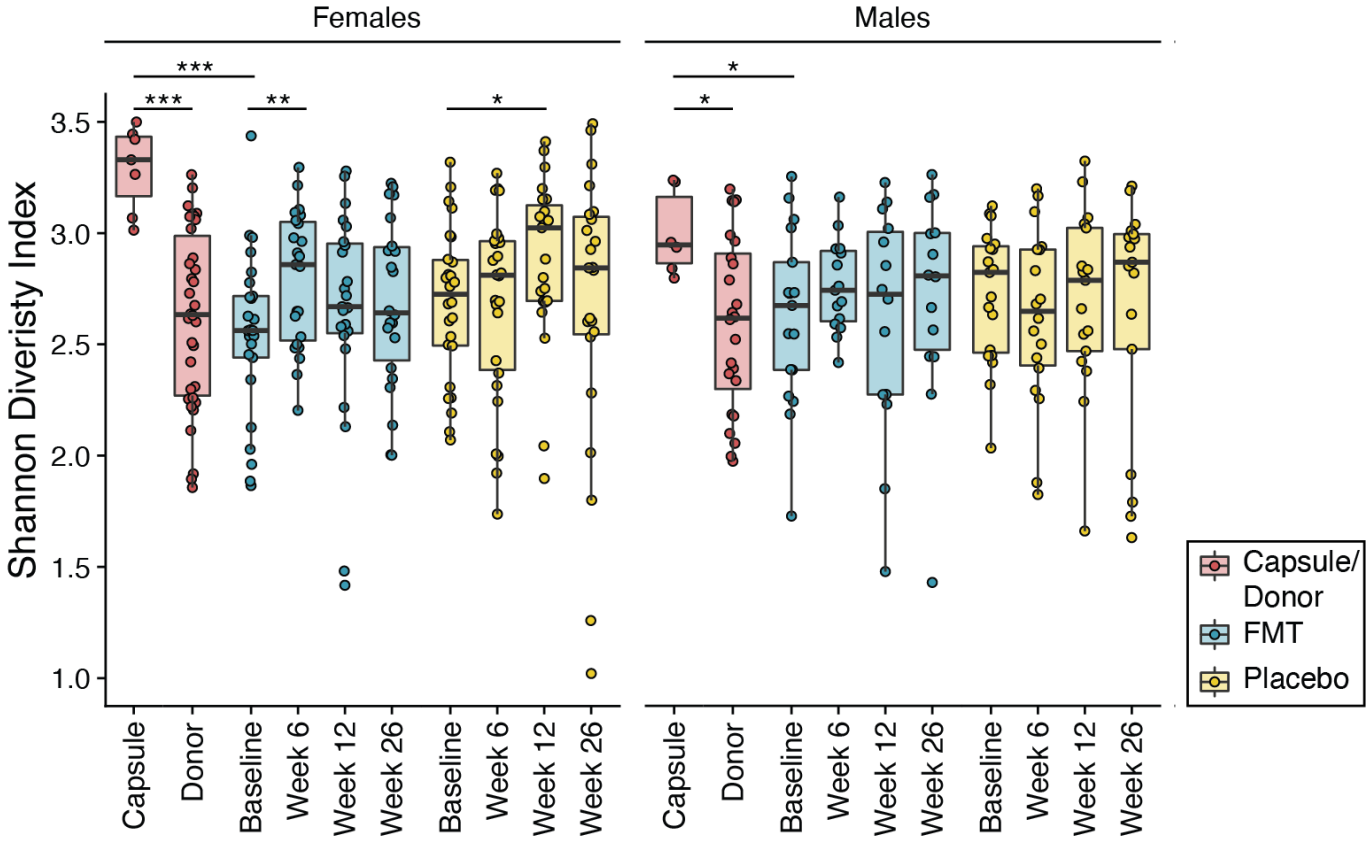
[1]The Liggins Institute, University of Auckland, Auckland, New Zealand

[2]The Broad Institute of MIT and Harvard, Cambridge, MA, United States

# One big strain competition experiment



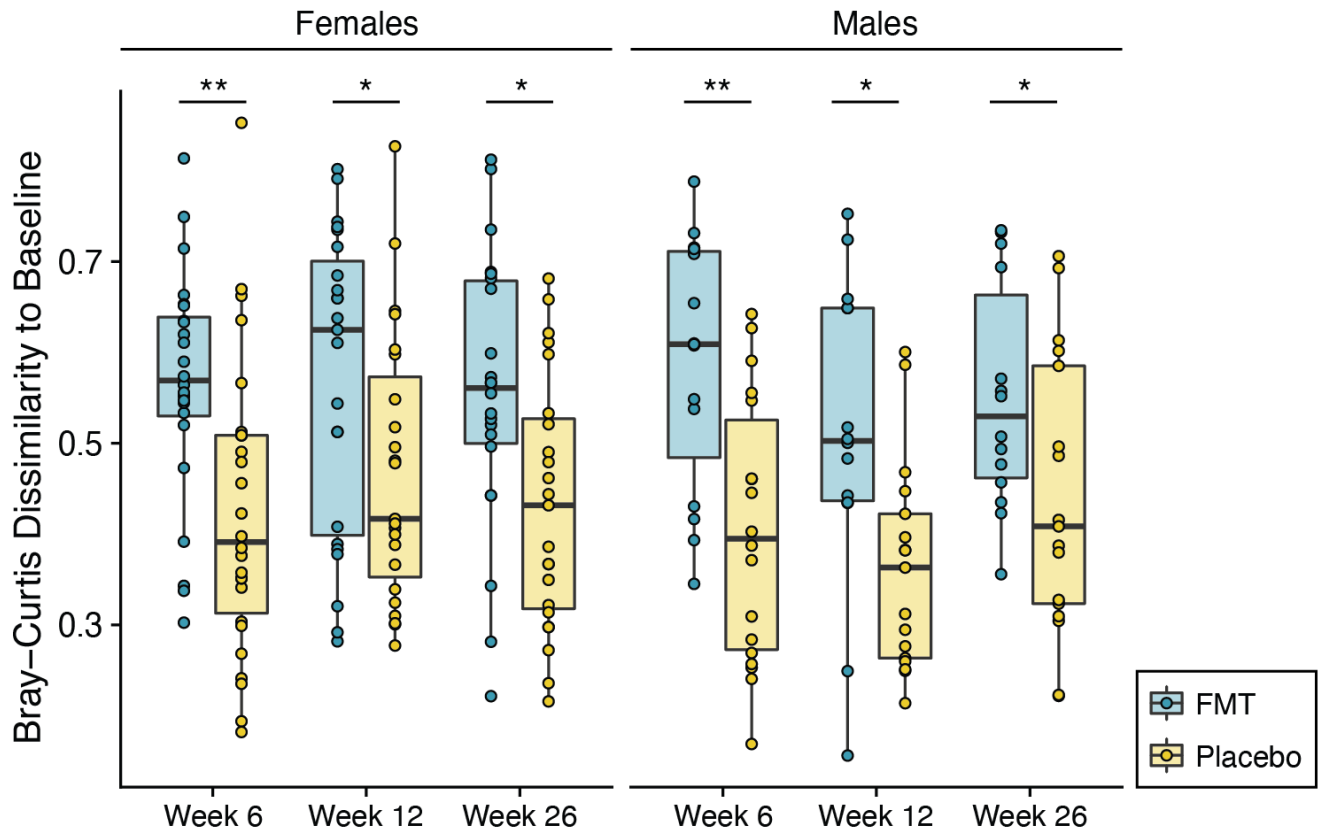
# Microbial diversity temporarily increased in female FMT recipients



# FMT shifted the microbial community structure which was sustained long-term

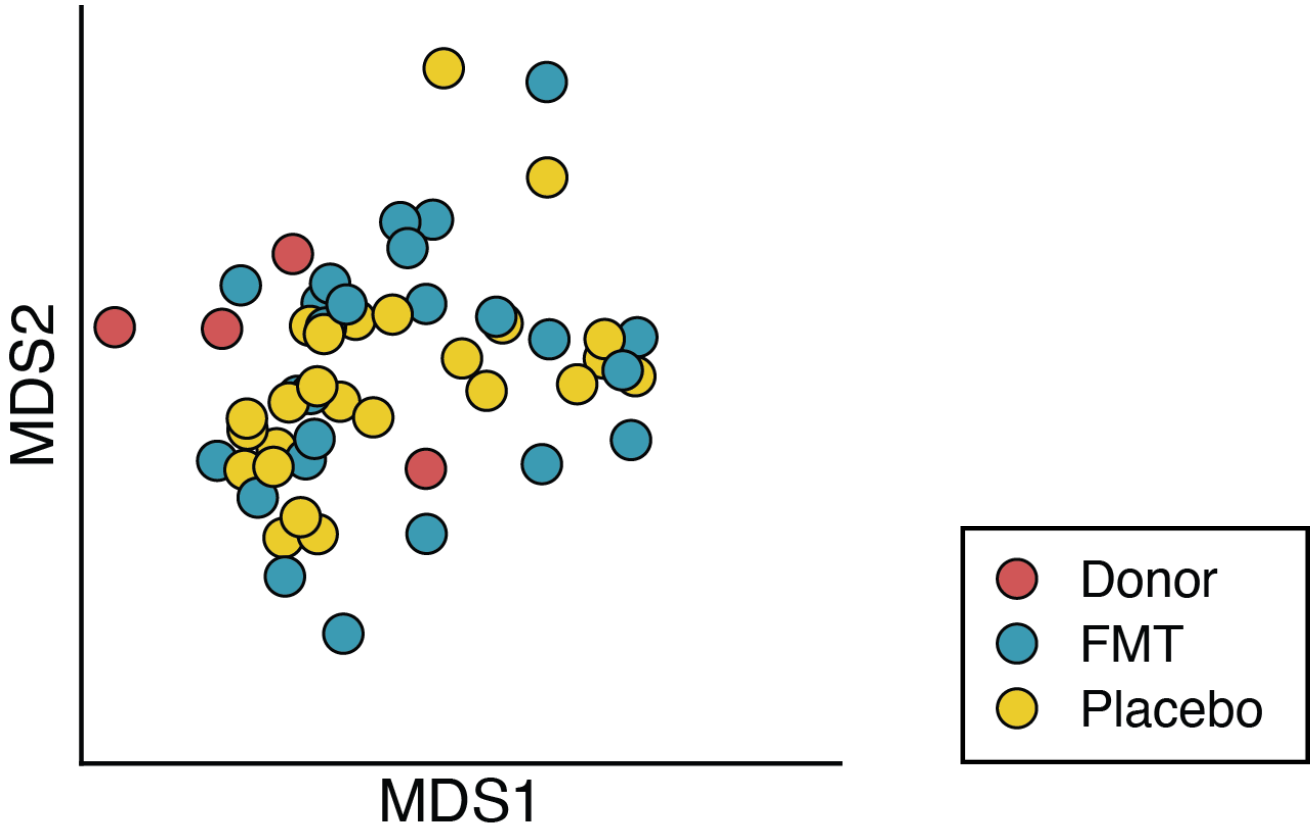
Less similar to BL

More similar to BL



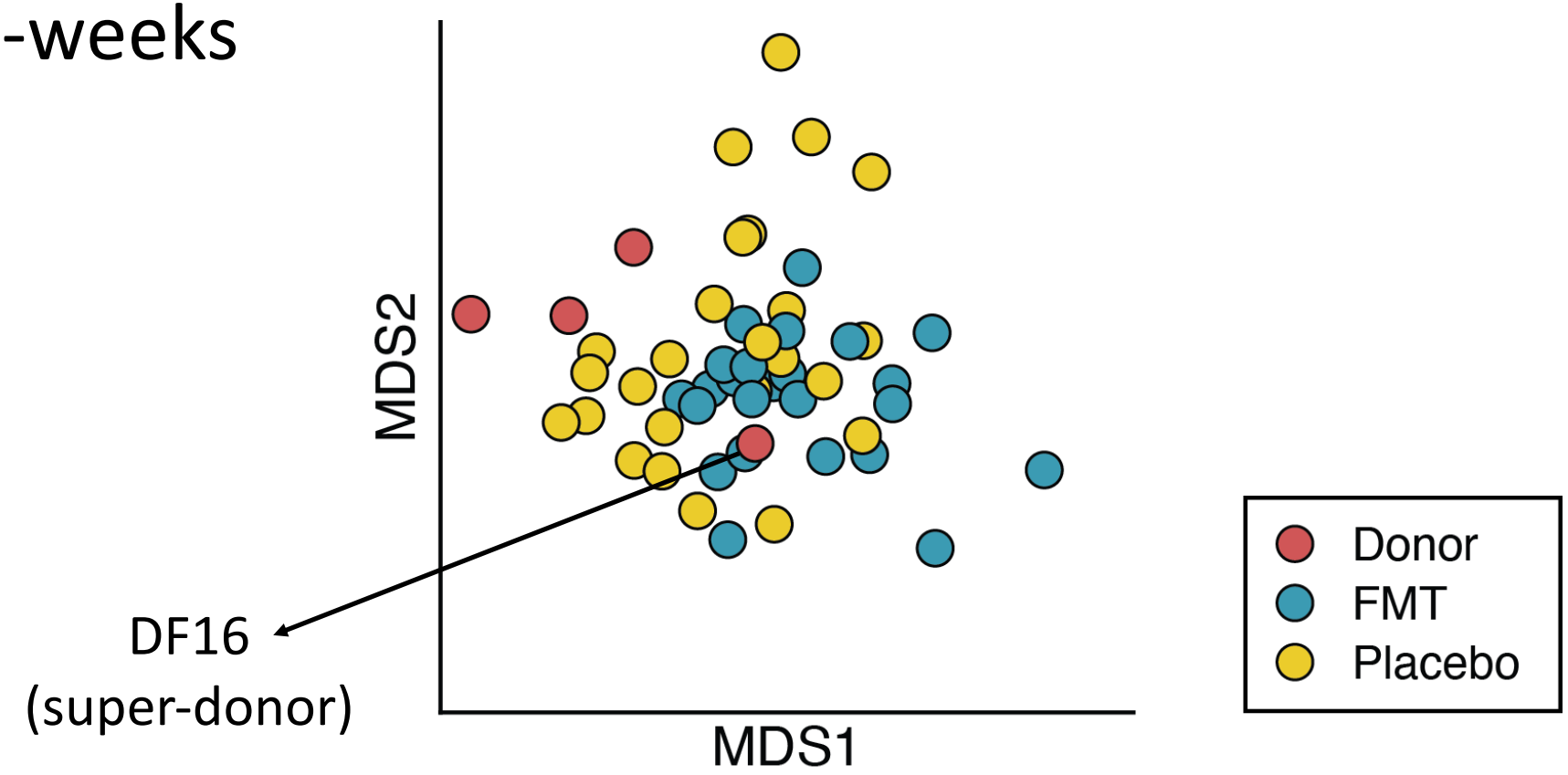
# Female Microbiomes

Baseline



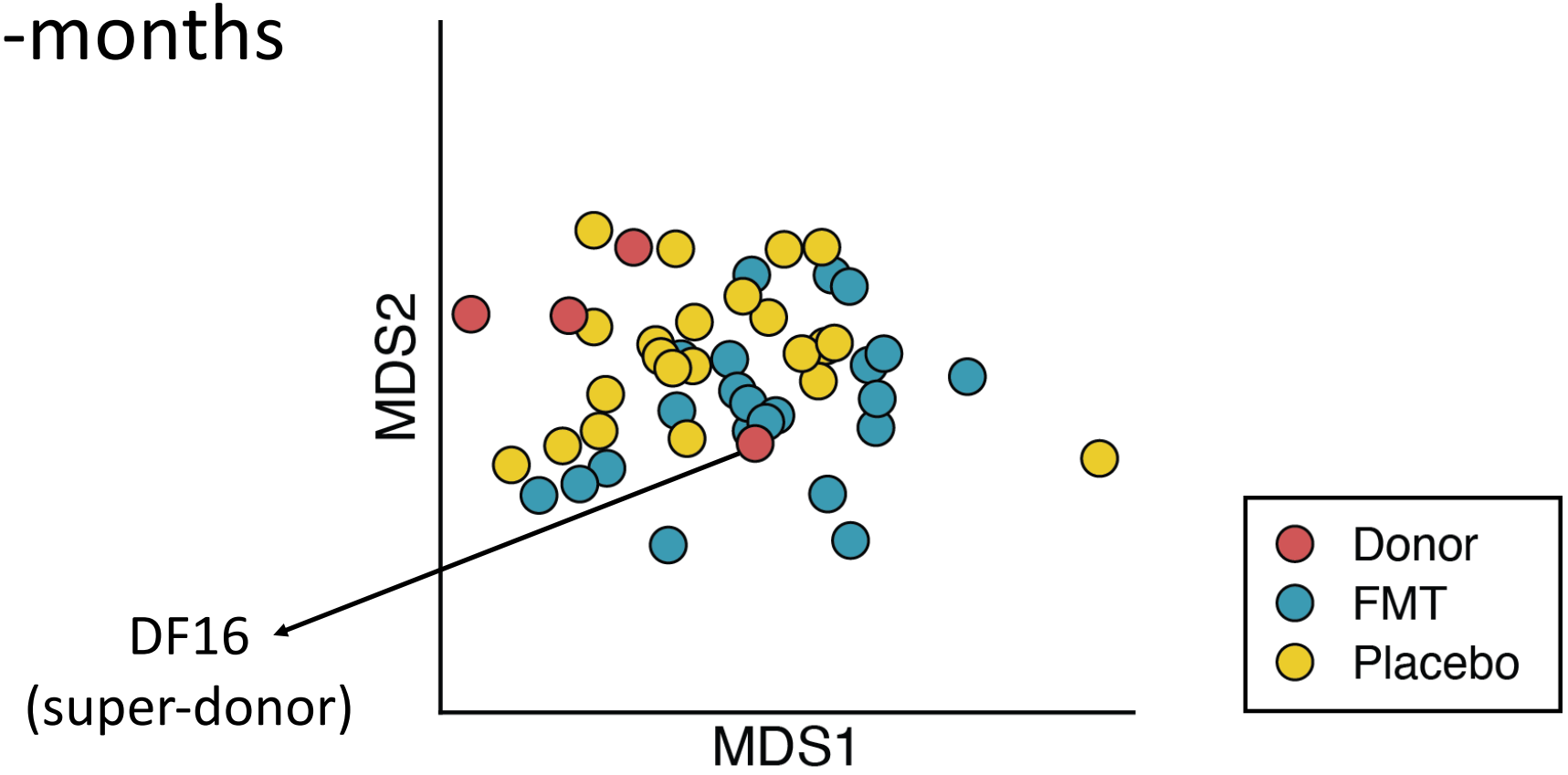
# Female Microbiomes

6-weeks



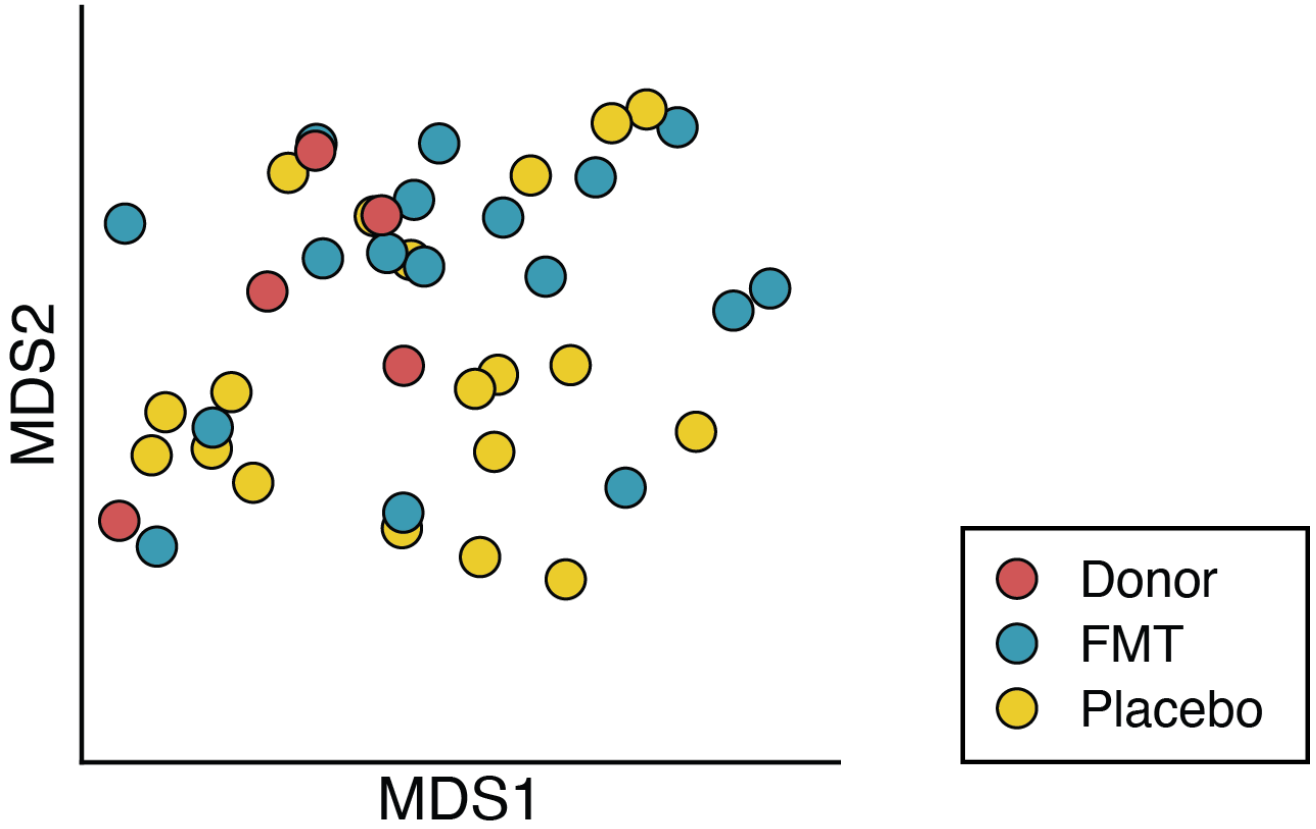
# Female Microbiomes

6-months



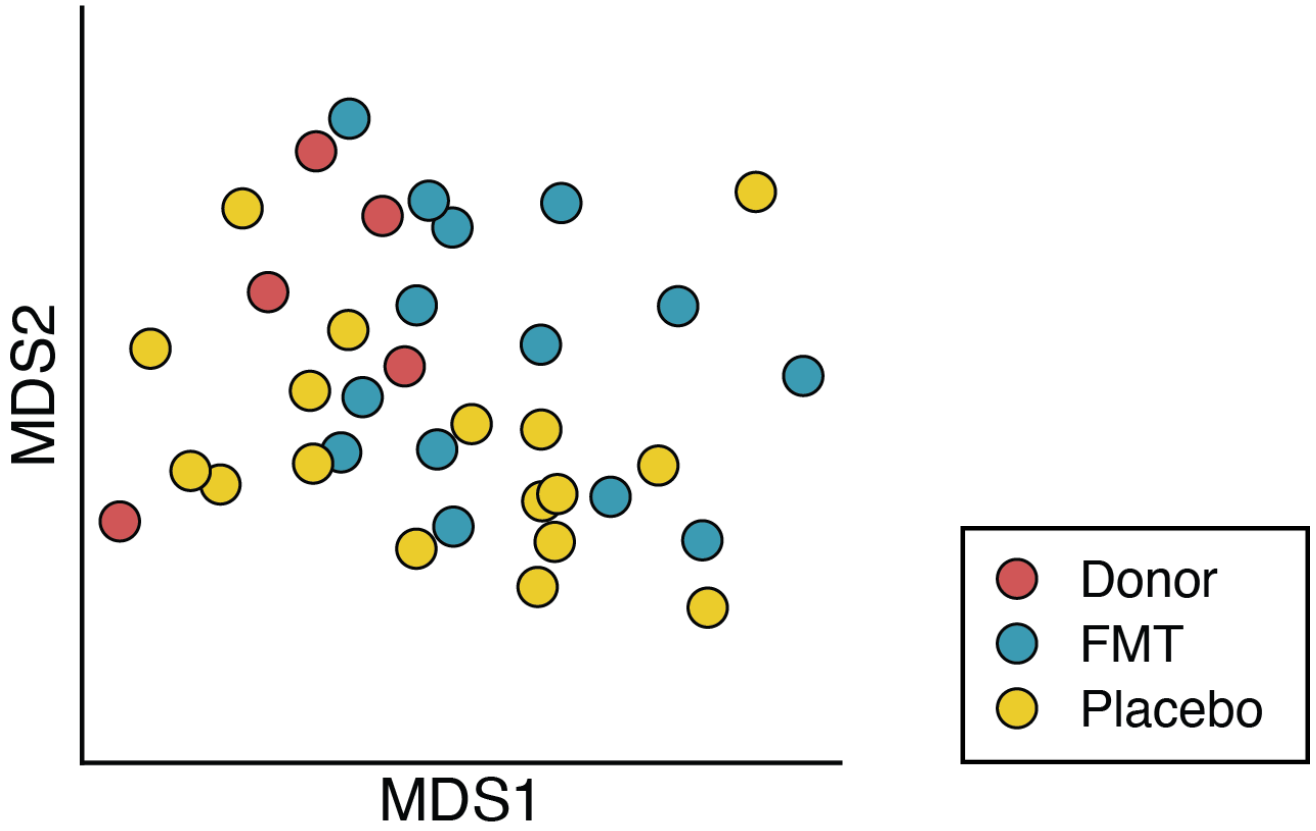
# Male Microbiomes

Baseline



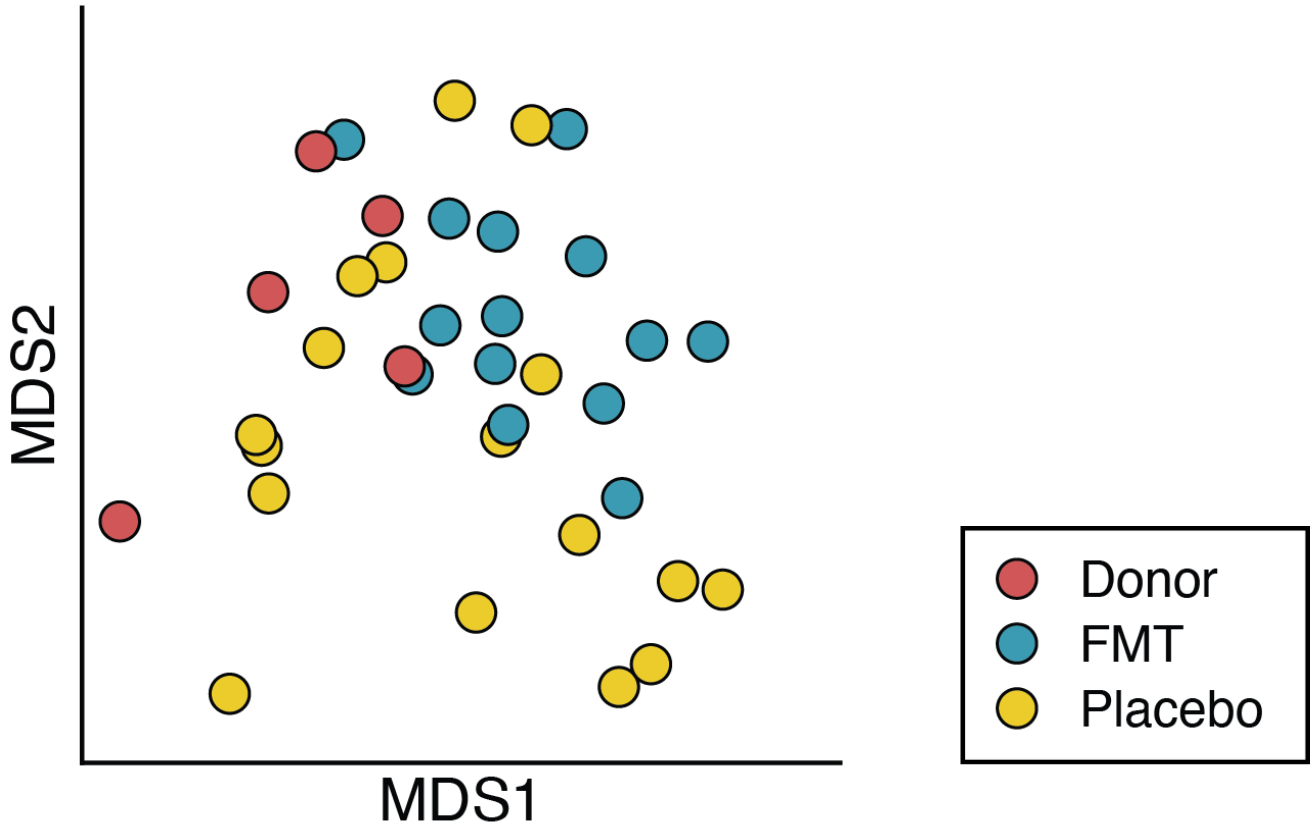
# Male Microbiomes

6-weeks

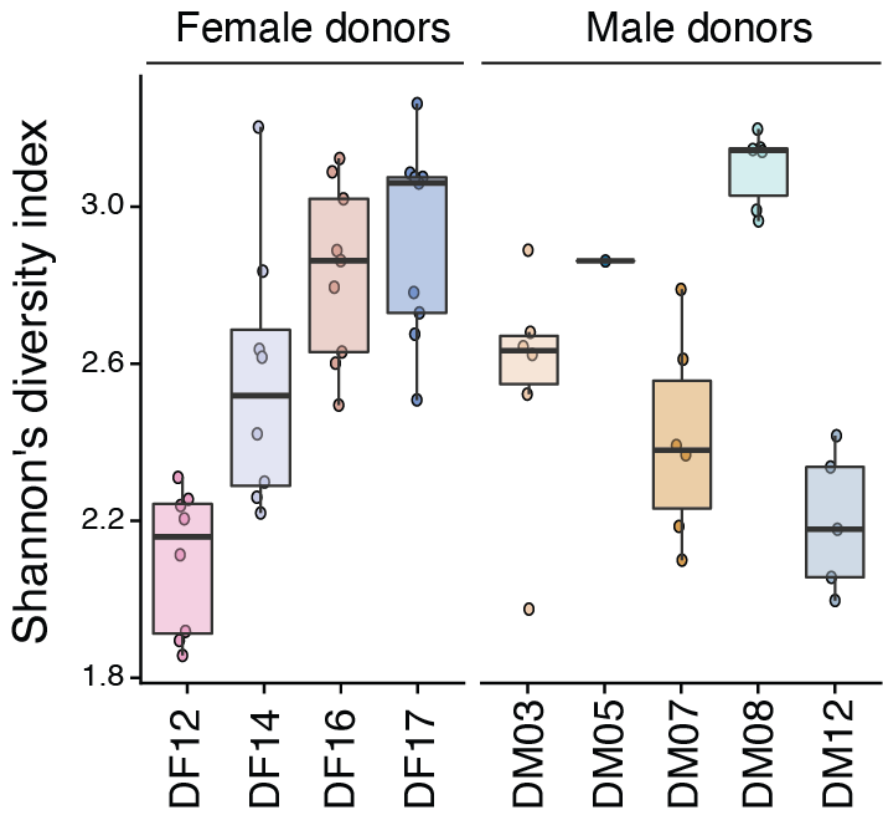


# Male Microbiomes

6-months



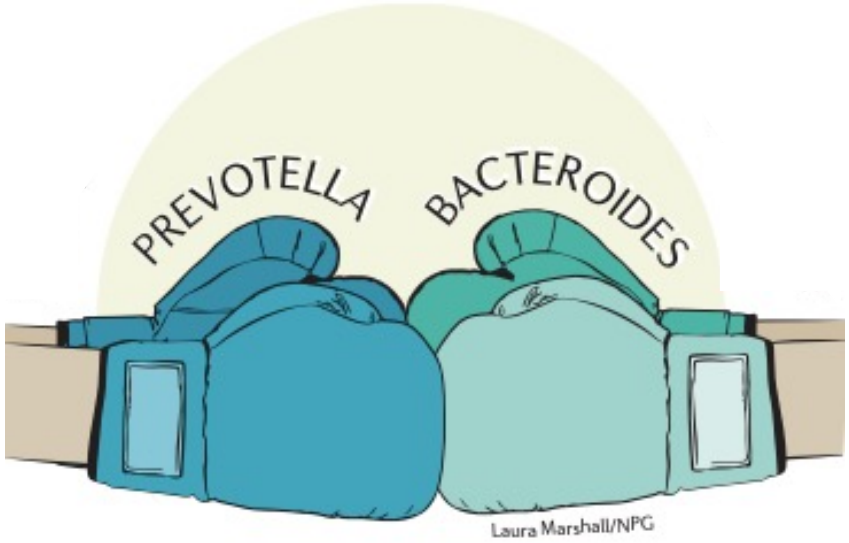
# DF16 had relatively high microbial diversity



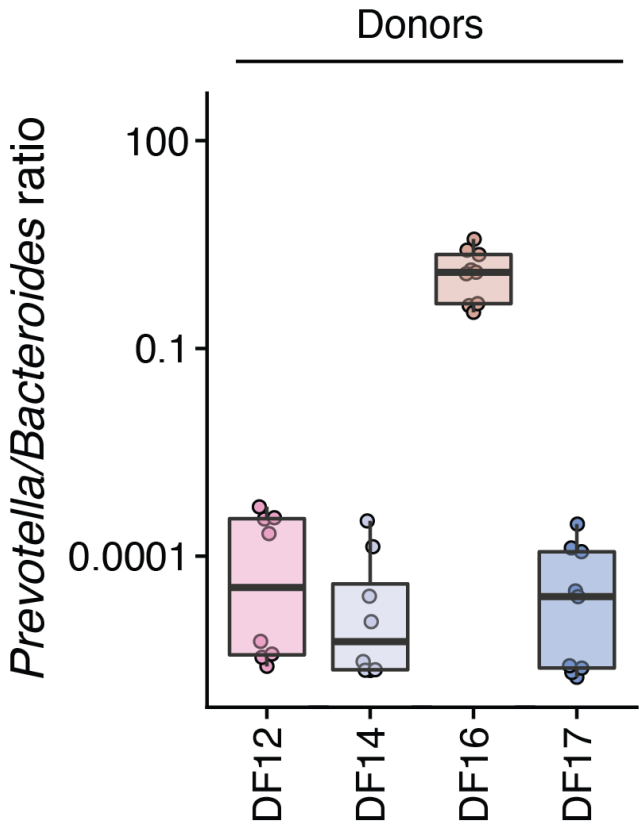
# *Prevotella/Bacteroides* ratio

*Prevotella*-type:

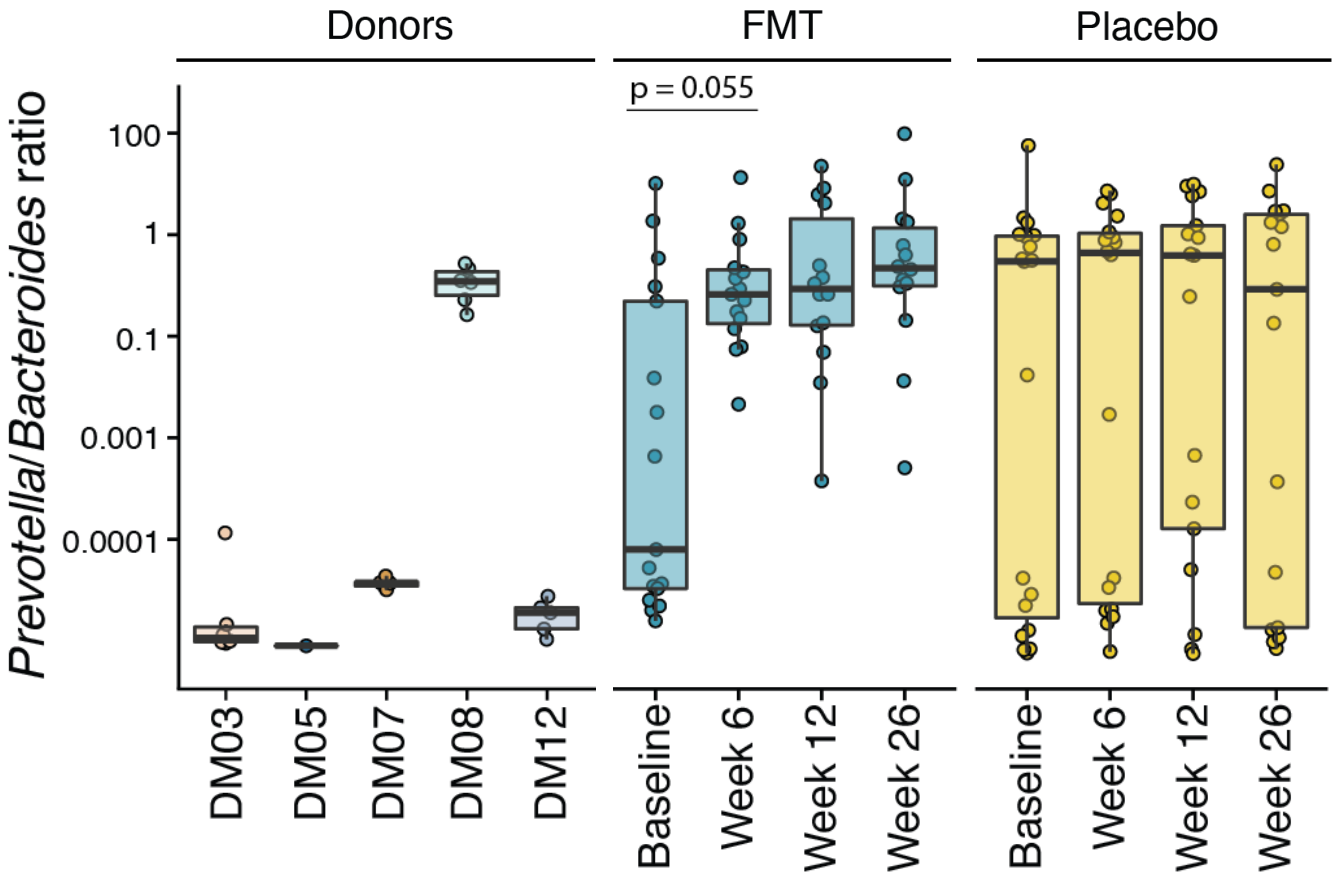
- More common in non-Western populations
- Associated with plant-rich, high fiber diets
- Lose weight effectively on high fiber diets



# Females: *Prevotella/Bacteroides* ratio

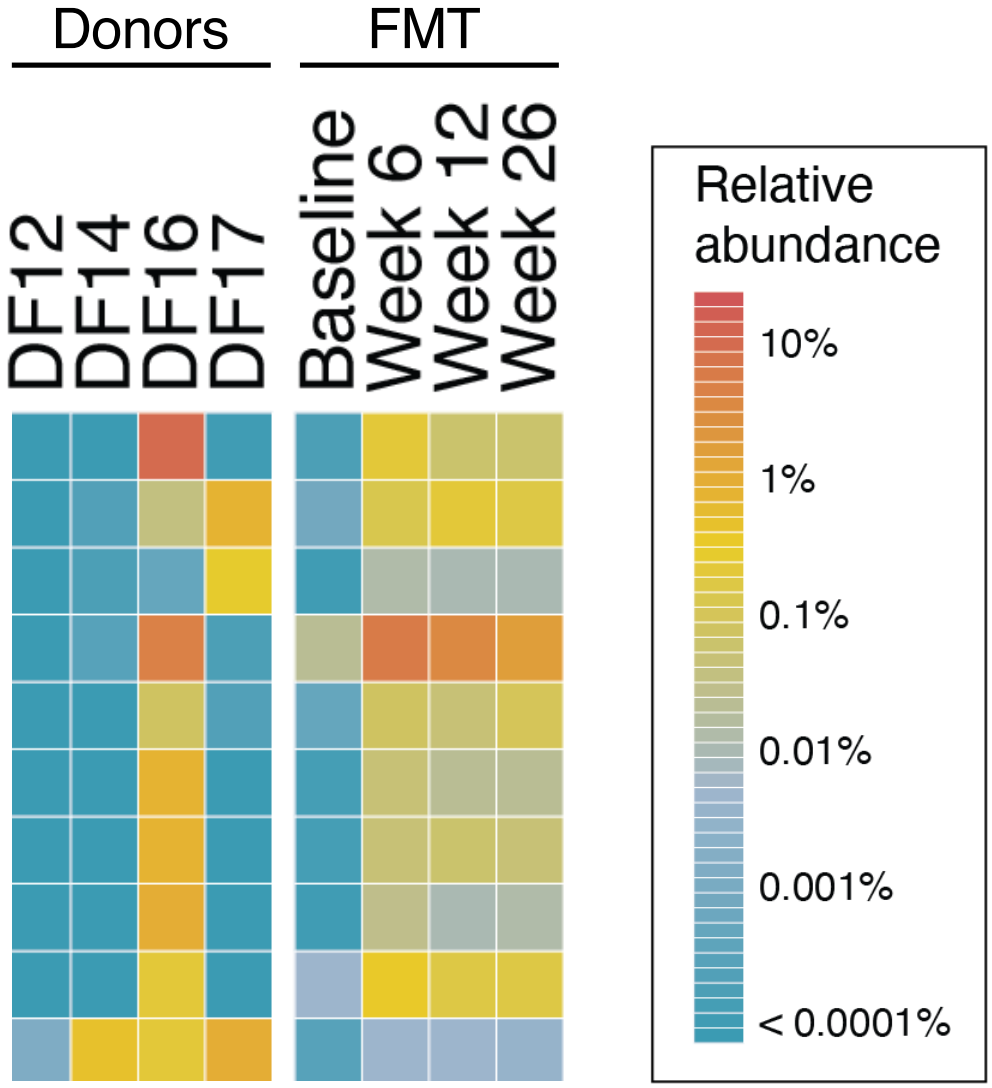


# Males: *Prevotella/Bacteroides* ratio

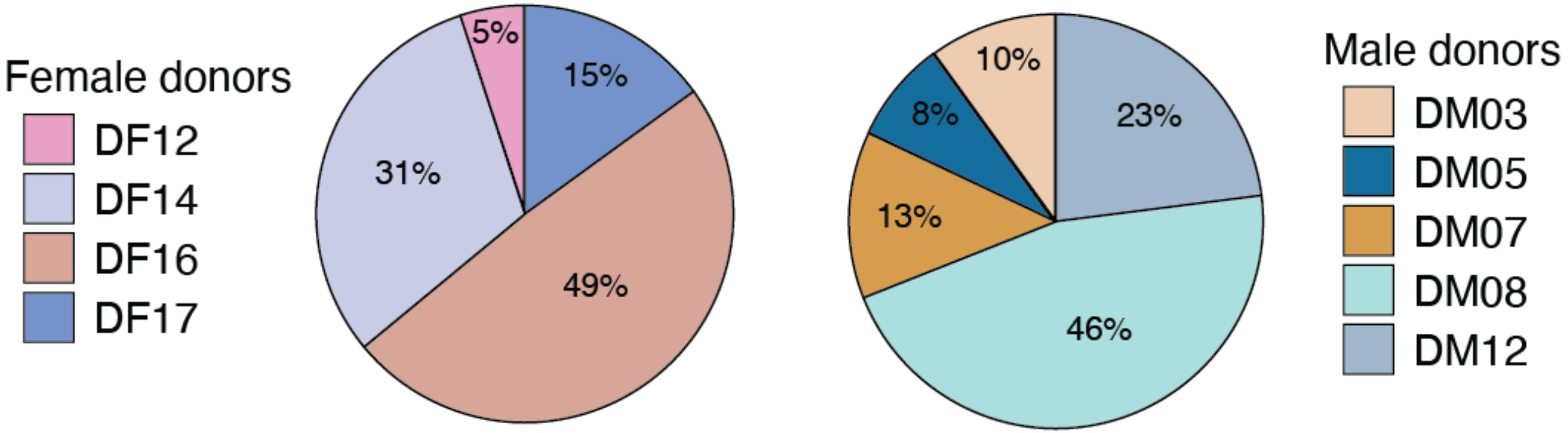


# Species enriched

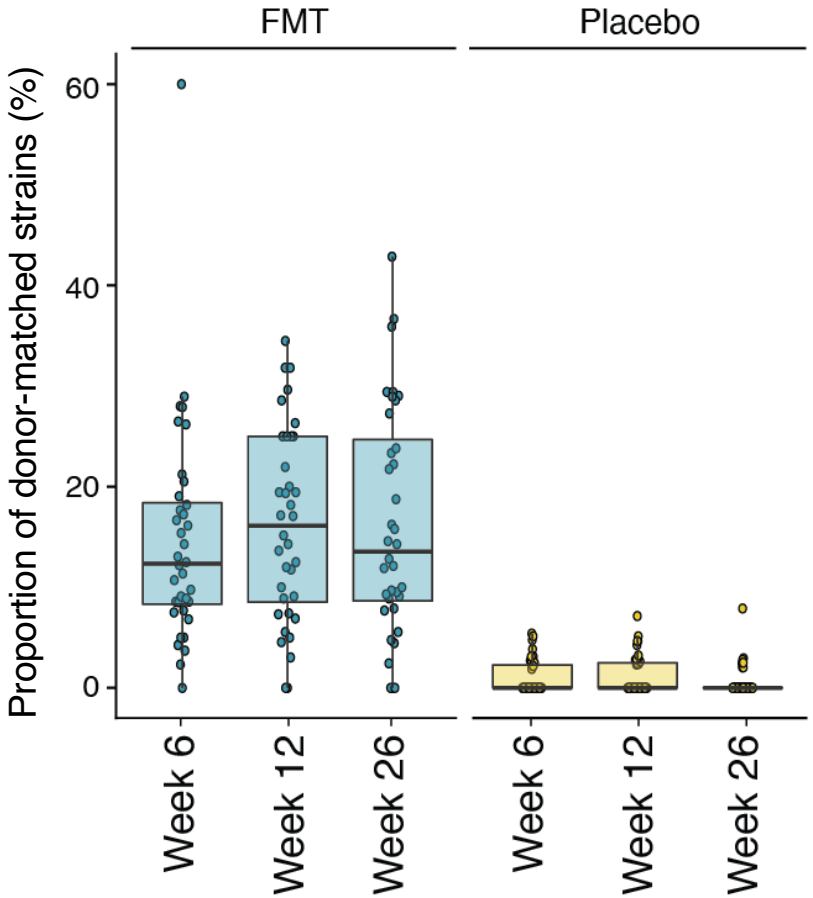
*Megamonas unclassified*
*Bacteroides finegoldii*
*Bacteroides salyersiae*
*Prevotella copri*
*Bacteroides faecis*
*Megamonas hypermegale*
*Desulfovibrio piger*
*Megamonas rupellensis*
*Barnesiella intestinihominis*
*Ruminococcus lactaris*



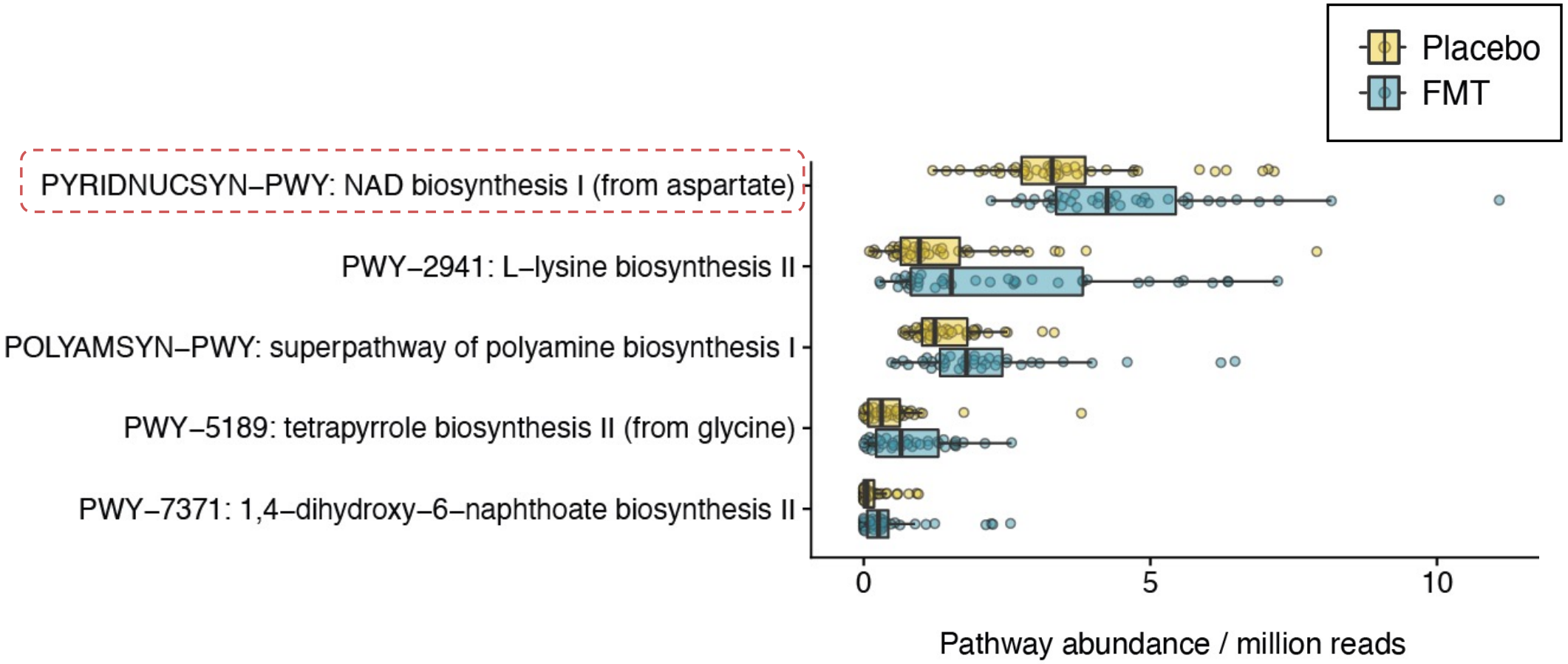
# Super-donor dominates strain engraftment



# Donor engrafted strains are retained long-term



# Microbial pathways that ↑ post-FMT



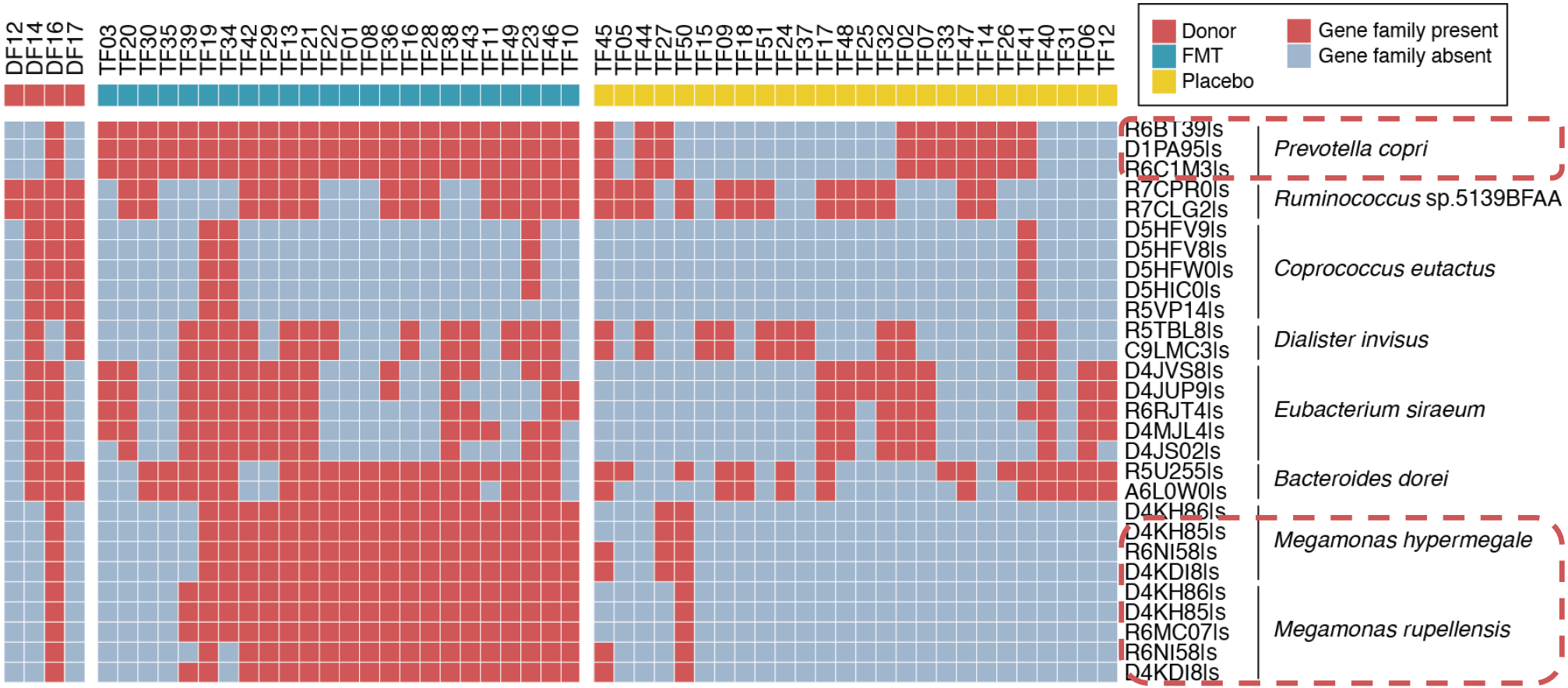
# NAD metabolism implicated in metabolic disorders

- Nicotinamide adenine dinucleotide (NAD) has 2 broad functions:
  - Coenzyme for glycolysis, fatty acid oxidation & oxidative phosphorylation
  - Rate-limiting substrate for sirtuin enzymes (deacetylate/silence target genes)

- NAD intricately involved in energy balance regulation
  - Acts as an energy sensor

- NAD levels are ↓ in obesity & diabetes
  - Lower ATP production
  - impaired energy metabolism regulation


# Strain engraftment from super-donor (DF16) provided genes involved in NAD biosynthesis



# Summary of microbiome findings

- FMT alters the structure and function of the gut microbiome for up to 6 months
- Not all stool donor microbiomes are equal
- Super-donor microbiome characterised by:
  - High microbial diversity
  - Prevotella-dominant microbiome
  - Unique taxa (e.g. *Megamonas* species)

- FMT recipients display variable levels of FMT engraftment
  - Host factors e.g. diet, endogenous microbiome, immune response likely play a role

# Conclusions

- FMT alone is unlikely to be effective to treat obesity
- FMT may reduce visceral adiposity
- **FMT may be effective to treat metabolic syndrome**
- Future trials are needed to:
  - confirm these results
  - identify organisms and mechanisms that are responsible for mediating the observed benefits

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