Gut microbiome transfer methods differ in transfer efficiency and can impact model phenotypes

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MMRRC
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Background

- Gut microbiota (GM) varies widely among commercial suppliers.
- Variance in the GM can influence disease phenotype (IL10$^{-/-}$ IBD disease model).
- Causality is tested by transferring complex GM between mice.
- Embryo transfer (ET)-golden standard: **Expensive and require higher Expertise**
- Co-house (CH)-commonly used: **Ease of use at low cost, loss early stage GM**
- **Little is known about the efficacy of cross-foster (CF) in GM transfer.**

Hypothesis

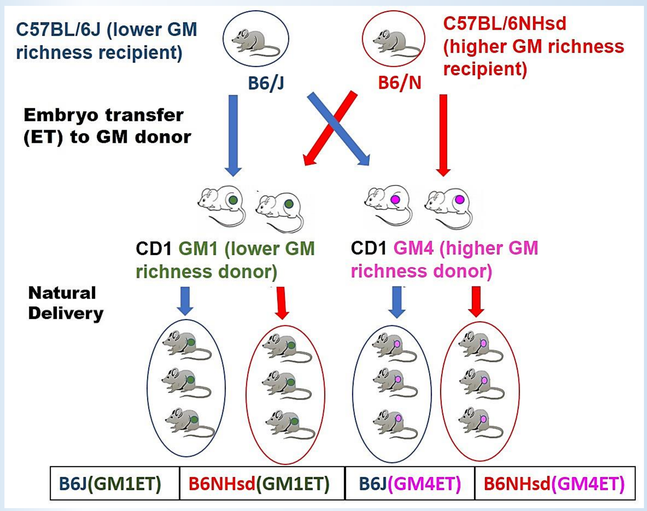
- GM transfer methods differ in transfer efficacy, with ET, cross-fostering, and co-housing decreasing in efficacy.
- Differences in the transfer efficacy will be correlated with differences in the phenotype of a GM-dependent model of inflammatory colitis.

Innovation

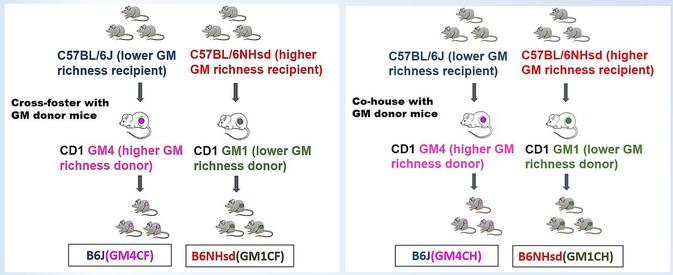
- Few data are available regarding the degree of GM transfer efficacy and influence on disease phenotype using different transfer methods.
- Data from animal models suggest that differences in richness between donor and recipient pre-transfer affect transfer efficiency, thus both directions of transfer were studied using each transfer method.
- The impact of recipient substrain on ET transfer efficiency was also assessed.

Experimental Design

- Group 1 – Embryo transfer (ET) gold standard (Transfer GM from conception)

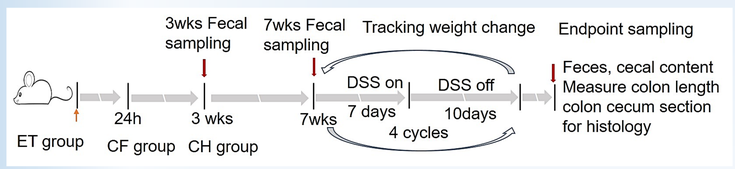


- Group 2 – Cross-foster (CF) GM recipient within 24h of birth to GM donor
- Group 3 – Co-house (CH) GM recipient with age-matched GM donors



- Donor GM compared to recipient GM at two time-points post-transfer using 16S rRNA amplicon sequencing of fecal DNA

DSS-induced chronic colitis disease model



Acknowledgement

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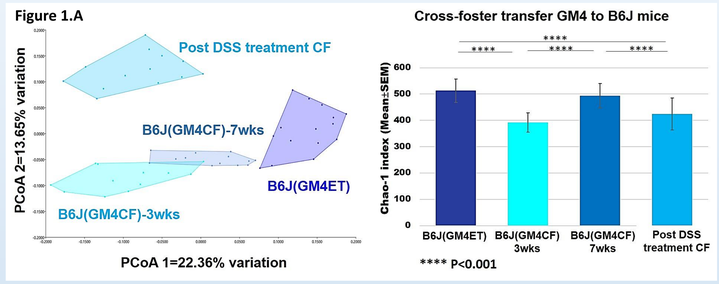
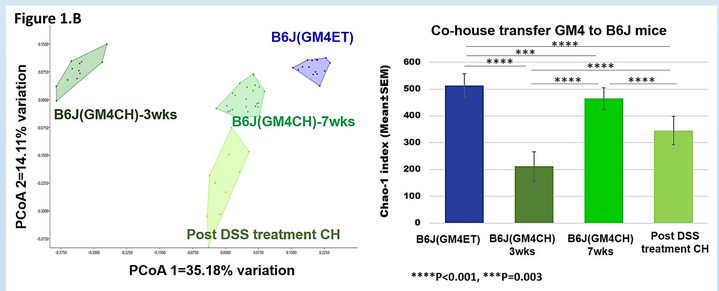
Transfer method influences transfer efficiency

Transfer high richness GM4 to B6J mice





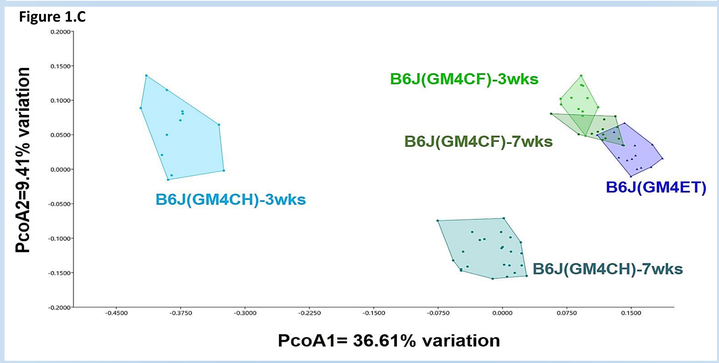
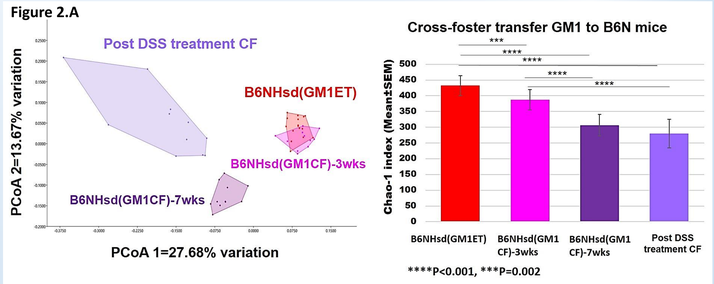
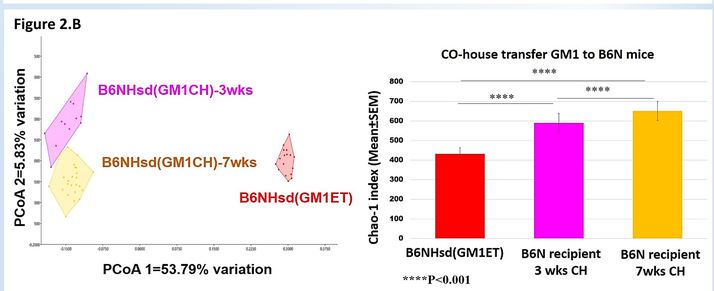


Figure 1. (A & B) Principal coordinate analyses (left) and bar charts showing mean (± SEM) Chao-1 richness index (right), show the variation between mouse groups generated using the ET gold standard and CF and CH methods. **(C)** Comparison of different transfer methods.

Transfer low richness GM1 to B6NHsd mice





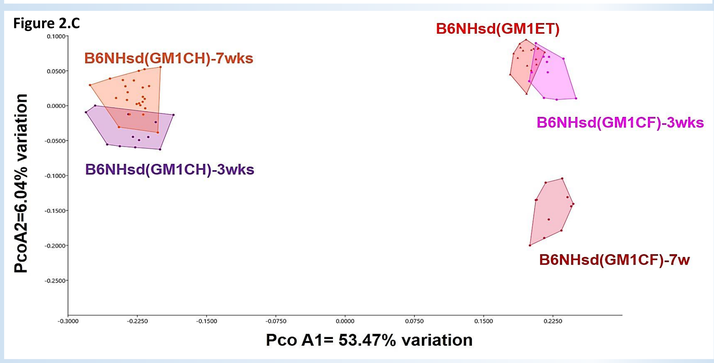


Figure 2 . (A & B) Principal coordinate analyses (left) and bar charts showing mean (± SEM) Chao-1 richness index (right), show the variation between mouse groups generated using the ET gold standard and CF and CH methods. **(C)** Comparison of different transfer methods.

DSS-induced weight change comparison using different transfer methods

Transfer GM4 to B6J mice

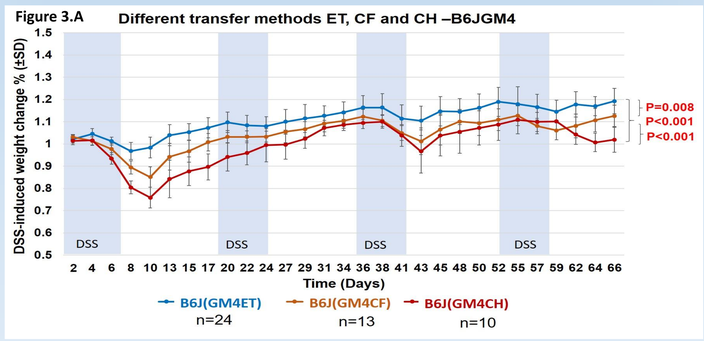


Figure 3 (A). DSS-induced weight change between ET, CF &CH methods to transfer GM4 to B6J mice. Two-way Repeated Measures ANOVA followed by all pairwise multiple comparison procedures (Student Newman-Keuls method).

Transfer GM1 to B6NHsd mice

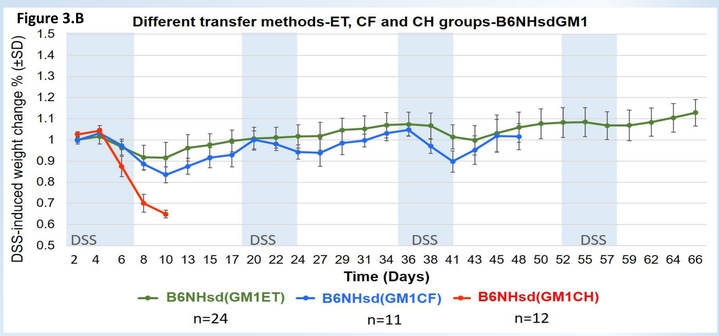


Figure 3 (B). DSS-induced weight change between ET, CF &CH methods to transfer GM1 to B6NHsd mice. Two-way Repeated Measures ANOVA followed by all pairwise multiple comparison procedures (Student Newman-Keuls method). (Statistic analysis of different groups within 10 days: P<0.05)

DSS-induced weight change (ET group)

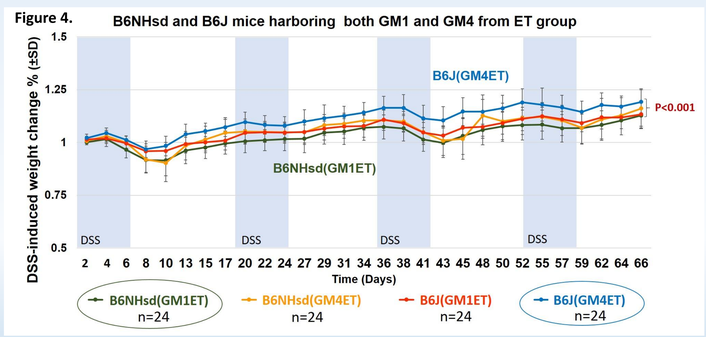


Figure 4. DSS-induced weight change between different groups using ET method . Two-way Repeated Measures ANOVA followed by all pairwise multiple comparison procedures (Student Newman-Keuls method).

Conclusions

- For both directional transfers, gut microbiota (GM) transfer efficiency was influenced by the transfer method. When compared to the gold standard ET method, CF had better transfer efficiency than CH.
- Recipient mice generated using different transfer methods showed differential susceptibility to DSS-induced weight change. The ET group had significantly less weight change compared to the CF and CH groups. Mice in the CF group showed significantly less weight loss compared to the CH group.
- Transfer of a low richness GM via CH and CF to recipient mice exposed even briefly to a high richness maternal GM is largely ineffective.
- Our results highlights the need to consider the efficacy of GM transfer methods when attempting to transfer a disease phenotype.