



Comparisons of Microbiomes from US and European Populations Suggest that SER-109 may have Clinical Utility in Broad Geographic Locations for the Treatment of Patients with Recurrent *Clostridium difficile* Infection

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Introduction: SER-109, a first-in-class microbiome therapeutic, is an ecology of approximately 50 unique bacterial spore-forming Firmicutes fractionated from rigorously screened US-based stool donors. In a phase 1b/2 study of patients with recurrent *Clostridium difficile* infection (RCDI), 87% of 30 US patients achieved the primary endpoint of absence of recurrent *C. difficile*-associated diarrhea at 8 weeks. Three of four patients who did not meet the primary endpoint had transient diarrhea that resolved without antibiotic therapy and tested negative for CDI. Thus, 29/30 achieved clinical resolution without further antibiotic therapy (Khanna et al., J. Infect. Dis. 2016). However, the efficacy of SER-109 outside the US may depend on the similarity of the microbiomes in other patient populations to US microbiomes.

Aims: To evaluate the similarity of US and European microbiomes to assess if SER-109 has therapeutic potential in European populations.

Methods: We compared the microbiomes of healthy adult US and European populations using microbial sequencing data from fecal samples. The entire microbiota and the spore-forming fraction were both interrogated. Several microbiome metrics were assessed.

Microbiome metrics:

- Bacterial richness (α -diversity):** The diversity of bacteria present in a single sample was quantified by the number of unique phylogenetic clades observed.
- Bacterial composition (β -diversity):** The difference (diversity) between samples was measured with an unweighted UniFrac metric, which takes into account the phylogenetic similarity of bacteria present across samples. Differences across samples were visualized with principal coordinates analysis.

Healthy cohort fecal microbiota sequencing datasets compared:

WGS = whole genome shotgun; 16S V4 = 16S rRNA sequencing of V4 region
HMP = Human Microbiome Project; below, n indicates number of subjects

- HMP WGS:** U.S., n=139
- MetaHIT WGS:** Europe, n=38
- Seres healthy stool donors 16S V4:** U.S., n=7; 78 samples
- HMP 16S V4:** U.S., n = 281; 563 samples

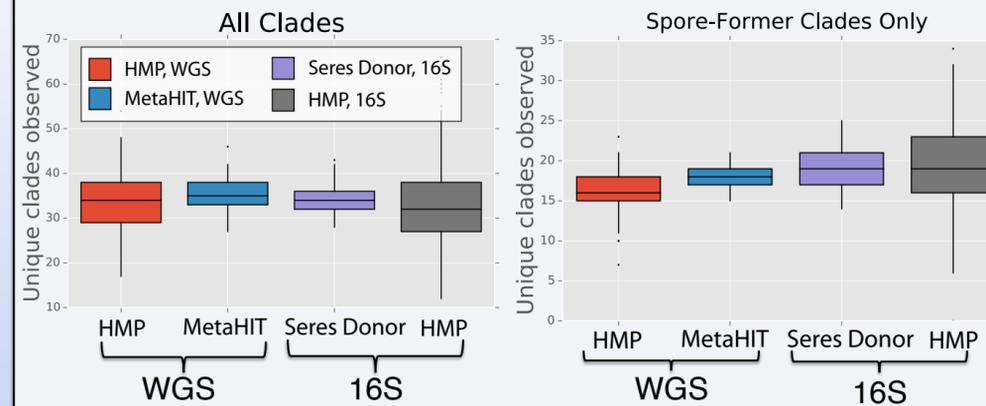
Clinical relevance of microbiome metrics: Post-treatment with SER-109 α - and β -diversity metrics among patients with recurrent CDI approach values seen in healthy individuals in HMP



16S V4 sequencing of patient samples from phase 1b/2 study is compared to HMP 16S V4 healthy cohort using α -diversity (left) and β -diversity (right) metrics.

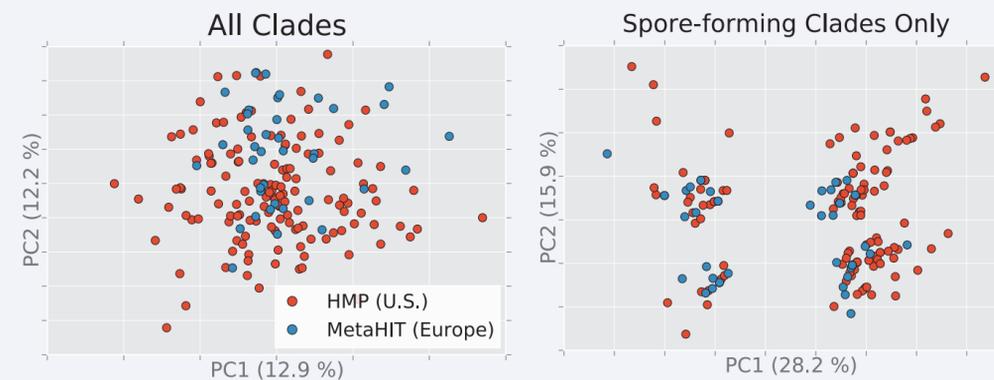
Results: Assessment of the transferability of SER-109 to European populations

Assessment 1: Healthy U.S. and European populations have a similar fecal bacterial richness (α -diversity)



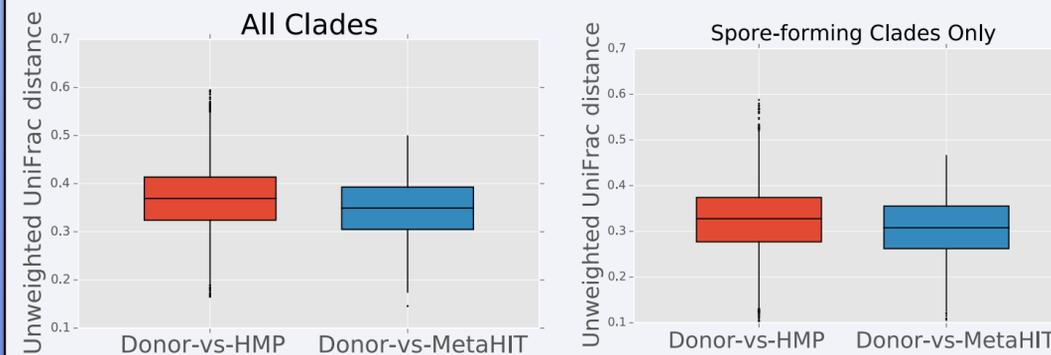
The bacterial richness of all clades (left) and spore-forming clades (right) is similar among US HMP WGS (34±6 and 16±6) and European MetaHIT WGS (35±4 and 18±2) datasets and among US-based Seres donors 16S (34±3 and 19±3) and US HMP 16S (33±8 and 19±5) datasets.

Assessment 2: Healthy U.S. and European populations have a similar fecal bacterial composition (β -diversity)



Principal coordinates analysis based on HMP WGS and MetaHIT WGS shows even mixing between US and European samples, indicating a similar phylogenetic composition of the microbiome in the populations. This is true when all clades (left) and spore-forming clades (right) are considered.

Assessment 3: SER-109 donor bacterial compositions (β -diversity) are equally similar to US and European populations



Median distances between donor microbiomes (16S) and HMP WGS and MetaHIT WGS are shown. (Smaller numbers indicate more similarity to donors.) The distributions for US and European microbiomes are similar both when all clades (left, 0.37±0.07 and 0.35±0.06) and only spore-forming clades (right, 0.32±0.07 and 0.30±0.07) are considered.

Assessment 4 and 5 (not shown): U.S. and European populations have similar prevalence and abundance (quantity) of phylogenetic clades.

Conclusions: Gut microbiota compositions from healthy US and European adult populations have a conserved ecology, supporting the potential therapeutic utility of SER-109 for the treatment of adults with RCDI in patient populations in Europe.