

Gut Microbiota and Associated Metabolites Play a Key Role in the Pathogenesis of the Obesity Phenotype of HFpEF

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This work is supported by a grant from the Israel Science Foundation (ISF).

01.09.2024

Disclosures

- I have no disclosures relevant to this talk



HFpEF, Obesity, and Gut Microbiota

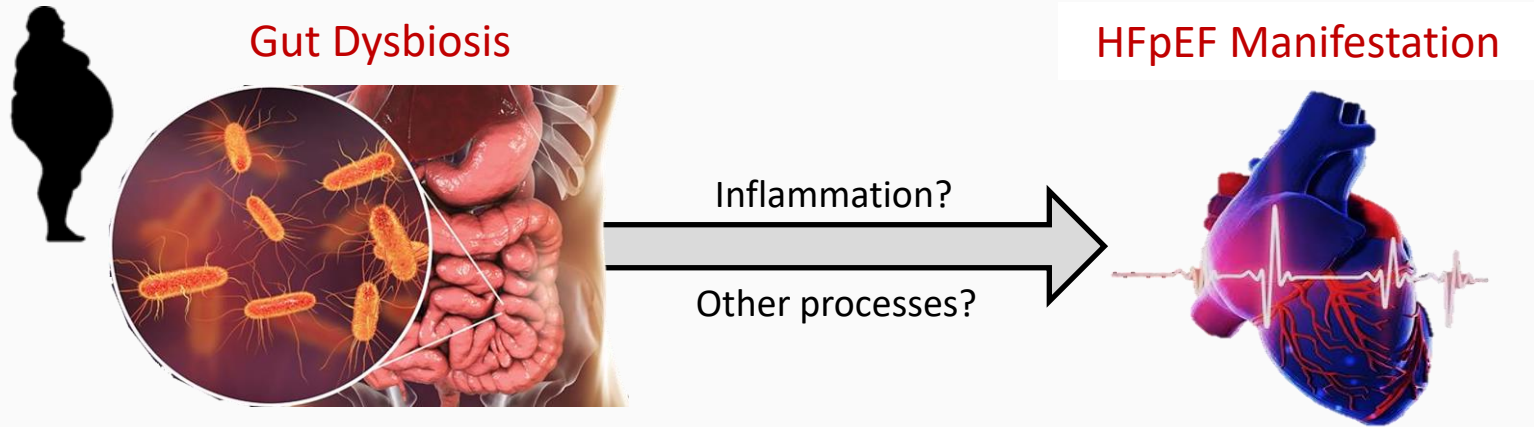
- HFpEF accounts for ~50% of HF cases with few proven therapies
- A heterogeneous disease that is largely driven by environmental factors and associated with multiple comorbidities
- Obesity-related HFpEF is the most common phenotype
- Gut microbial dysbiosis has been implicated in inflammation, insulin resistance, and obesity
- However, the involvement of the gut microbiota in the pathogenesis and progression of the obesity-related phenotype of HFpEF is unclear

Borlaug et al. JACC (2023); Desai et al. JACC HF (2023); Lam et al. Eur Heart J (2018); Lee et al. Circulation (2009).

Nemet et al. Cell (2020); Quigley et al. Nat Rev Gastroenterol Hepatol (2017); Buffa et al. Nature Micro (2021); Roberts et al. Nature Med (2018); Tang et al, Nat Rev Cardiol (2019); Ronen et al, Asleh. Compr Physiol (2024).

Study Hypothesis

- Gut microbial dysbiosis is important in the progression of the obesity phenotype of HFpEF

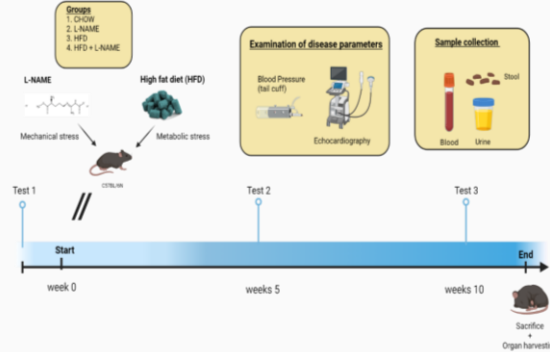
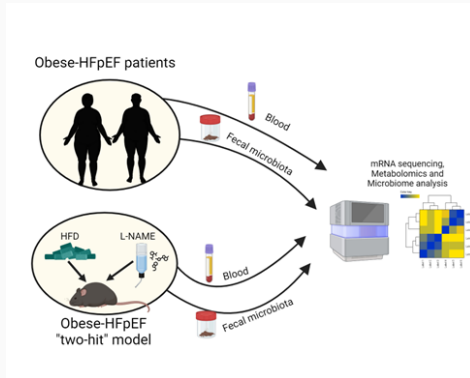


Study Design of the Obesity-Related HFpEF in Mice and Humans

Gut microbiome alterations in obese HFpEF mice and patients

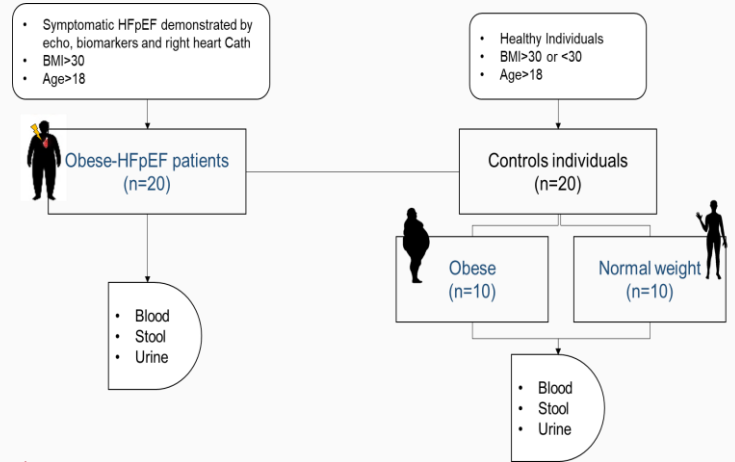
A “two-hit” mouse model of obesity-related HFpEF

A clinical phase: Study Design in humans



C57BL/6 mice divided into 3 groups:

- 1) Standard (chow) diet
- 2) HFD (60% calories)
- 3) Combined HFD + L-NAME (0.5 g/L in drinking water)

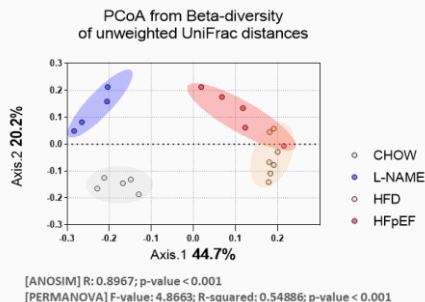


Schiattarella GG. et al. Nature (2019)

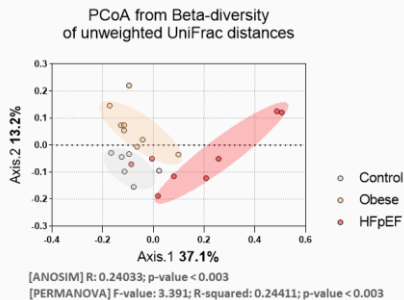
A Significant Association Between HFpEF and Gut Microbiome Composition

Beta-Diversity for Dissimilarities Between Groups

Mouse Model



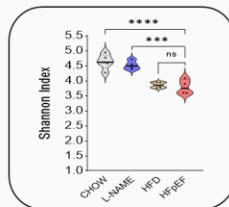
Humans



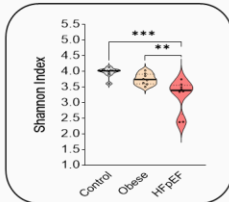
Alpha Diversity and Bacterial Relative Abundance

Alpha-Diversity for Community Variation Within a Group

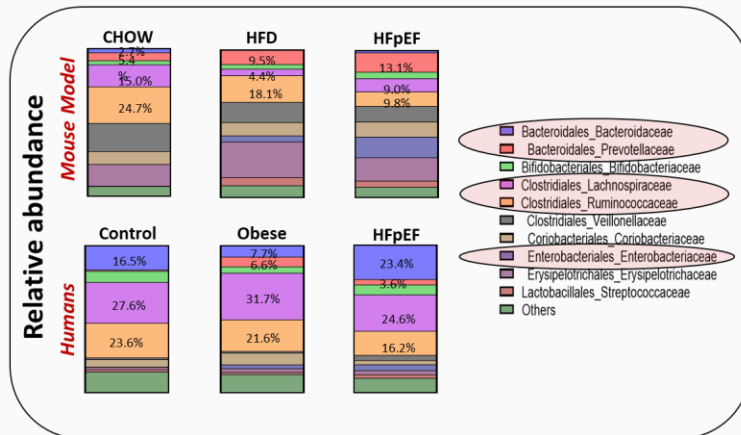
Mouse Model



Humans



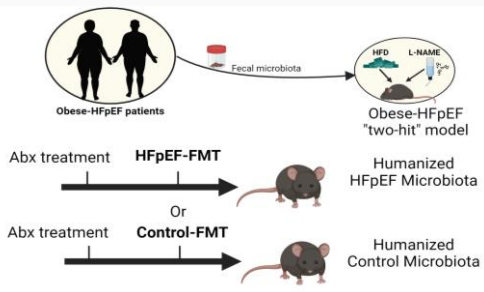
Relative Abundance of the most common bacterial families



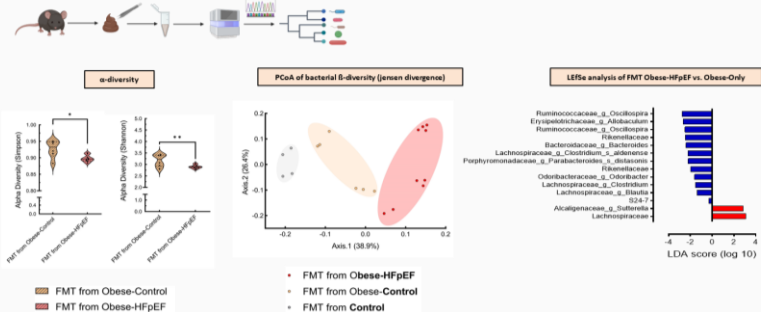
Worsening Diastolic Dysfunction in Mice After FMT from Obese-HFpEF Patients

Causative link between gut dysbiosis and HFpEF pathogenesis using FMT

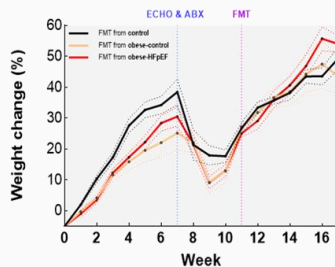
1. FMT after Extensive Abx Treatment



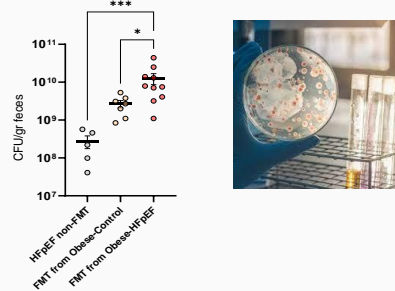
Gut microbiota of FMT in obese-HFpEF mice



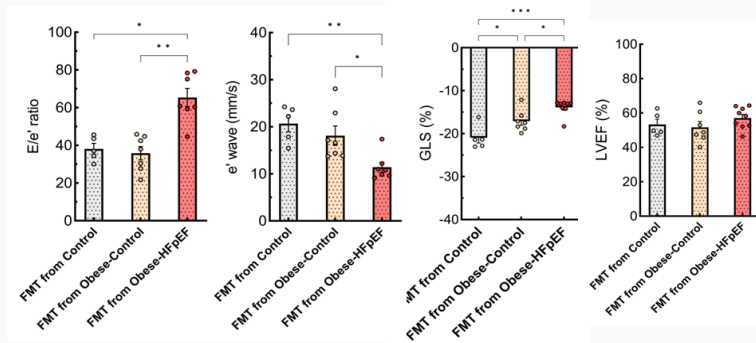
Body weight change



Blooming of Enterobacterial Species in the Gut of Different FMT Groups



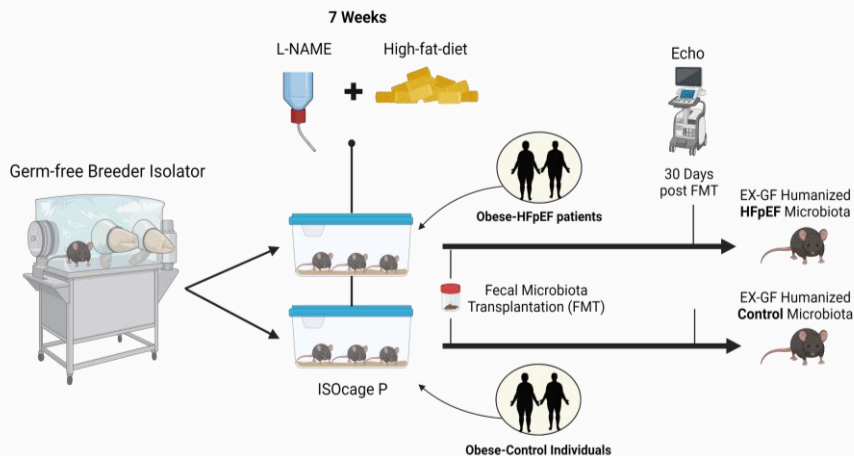
Echocardiographic assessment of diastolic and systolic function among FMT groups



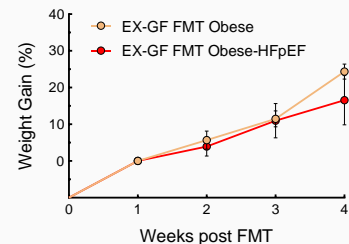
Worsening Diastolic Dysfunction in Germ-Free Mice After FMT from Obese-HFpEF Patients

Causative link between gut dysbiosis and HFpEF pathogenesis using FMT

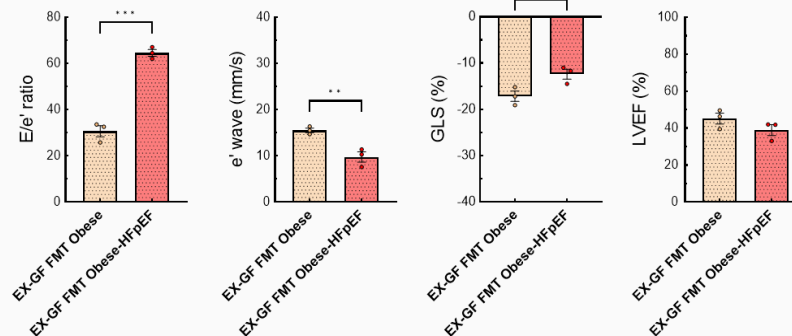
2. FMT in Germ-Free Mice with HFpEF



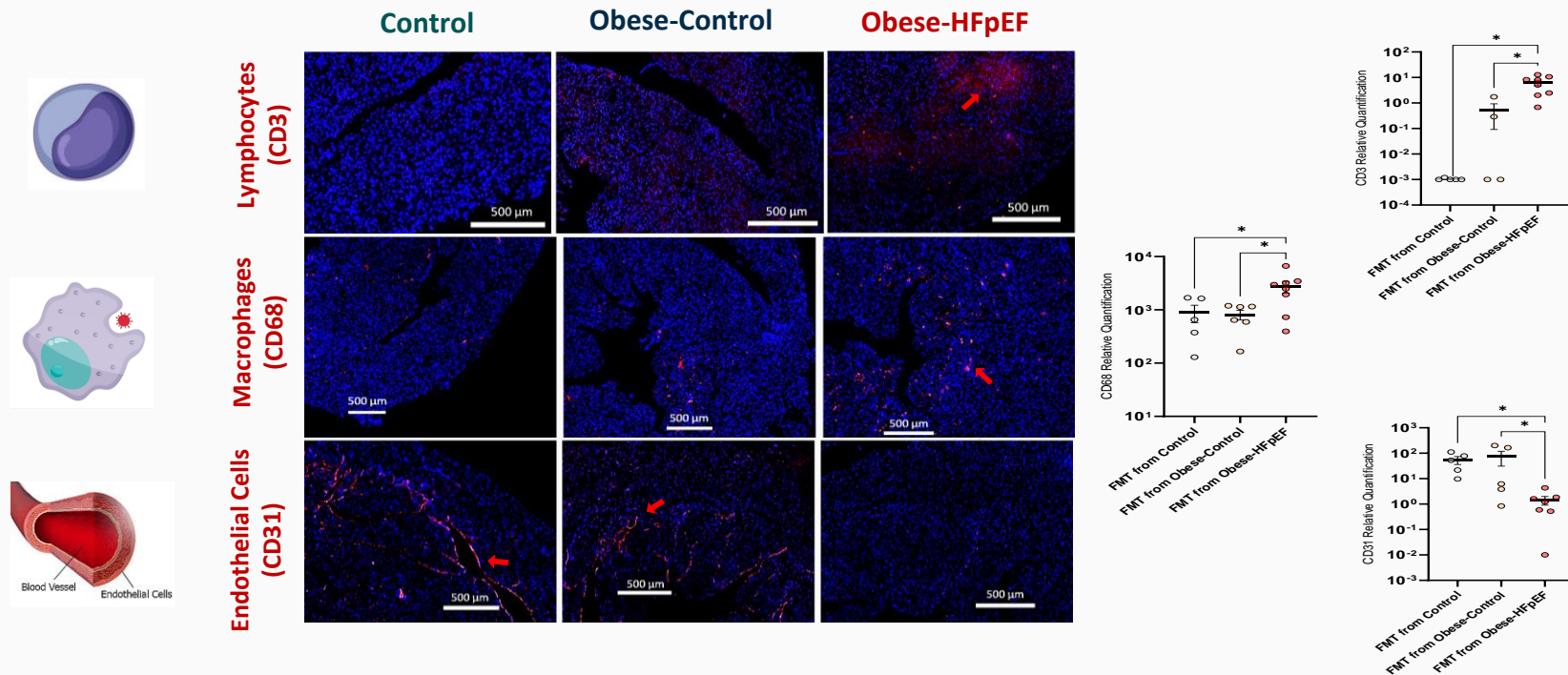
Body weight change between FMT groups



Echocardiographic assessment of diastolic and systolic function 1 month after FMT



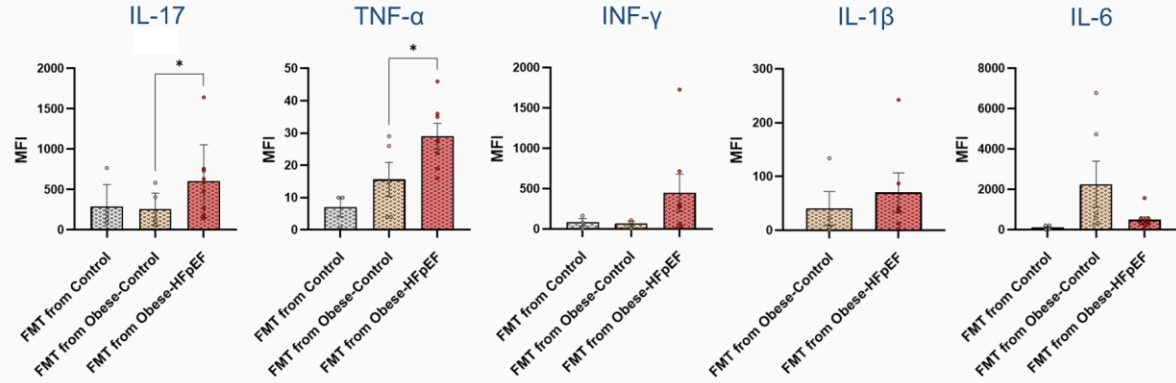
Increased Myocardial Inflammation and Endothelial Dysfunction after FMT from Obese HFpEF Patients to Mice



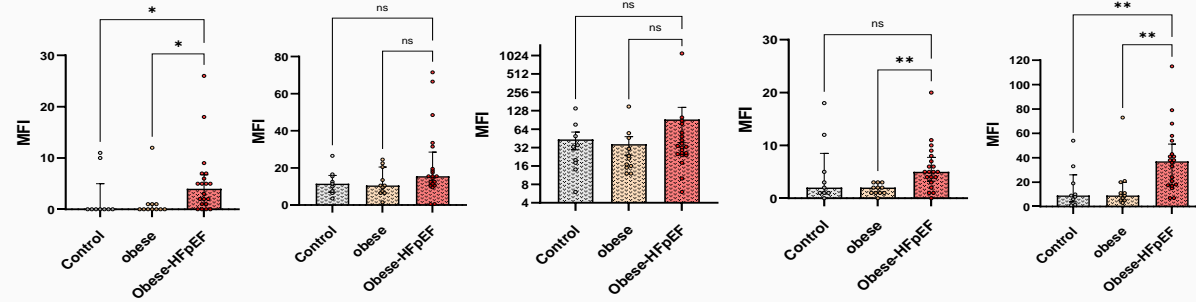
Increased Systemic Inflammation after FMT from HFpEF Versus Control Individuals as Observed in Human Samples



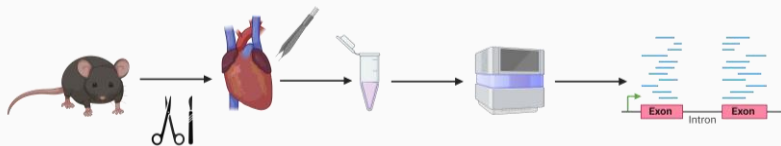
Mouse Model



Humans

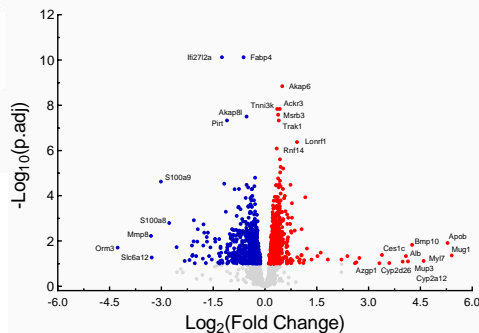
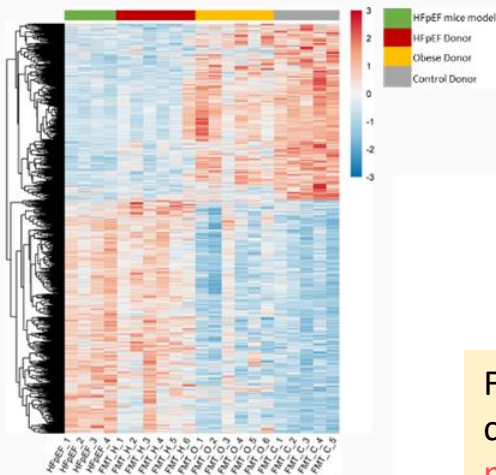


RNA-Seq Data Derived From Hearts of Mice Undergoing FMT from Obese-HFpEF Versus Control Subjects

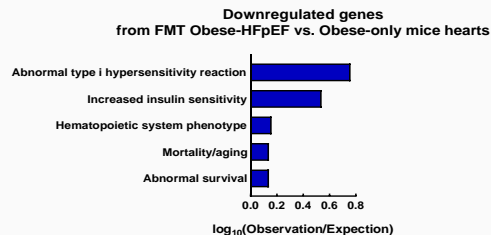
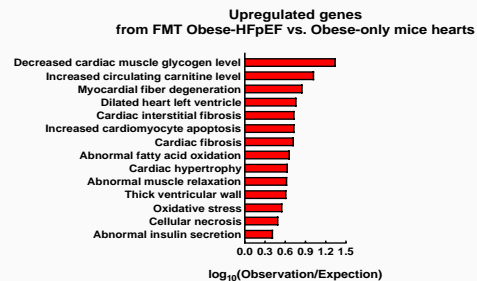


Heat maps showing differential gene expression

Volcano plot depicting the fold difference in gene expression levels

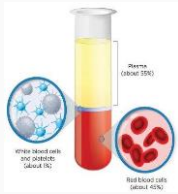


Mammalian Phenotype Ontology (MPO) of Transcriptome Data



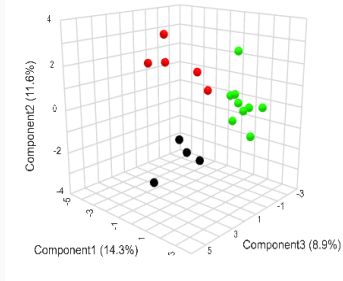
FMT from obese-HFpEF patients to mice was accompanied by elevated cardiac mRNA levels of **hallmark hypertrophic, fibrosis, and inflammatory markers** as compared to FMT from obese non-HFpEF subjects.

Metabolomics of Mice Plasma and Heart Tissue after FMT from Obese HFpEF Versus Control Individuals



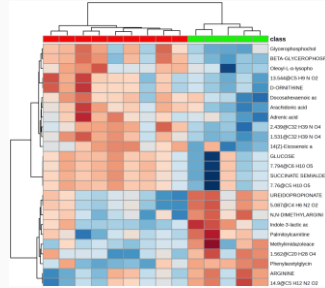
Plasma

sPLSDA

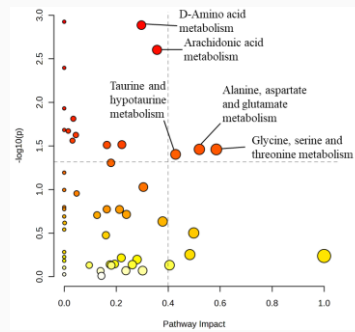


■ FMT Control
■ FMT Obese-Control
■ FMT Obese-HFpEF

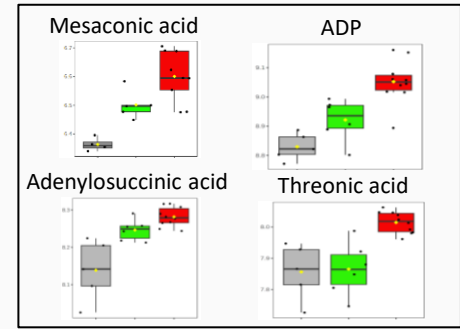
Heatmap



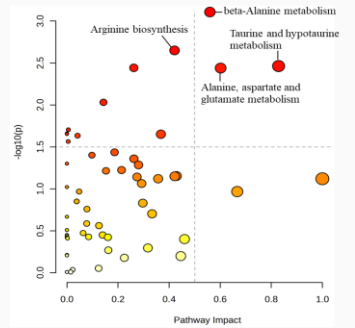
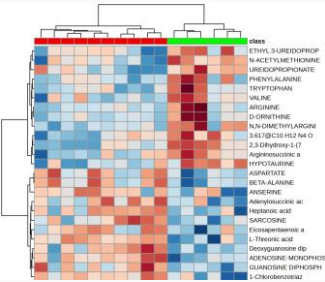
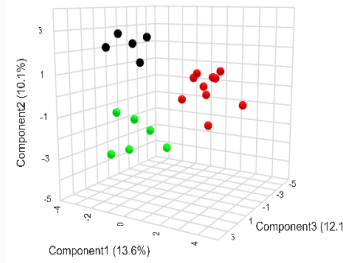
Pathway analysis



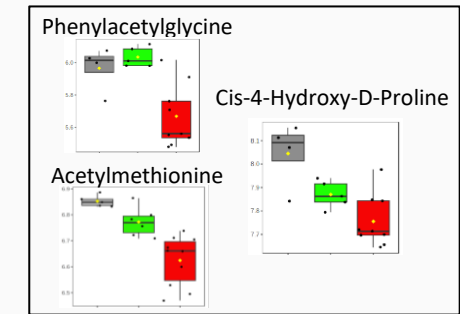
Top Upregulated ↑



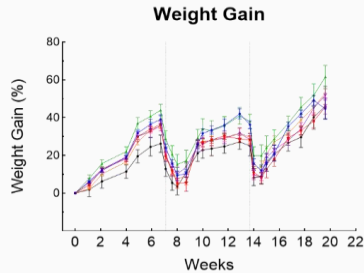
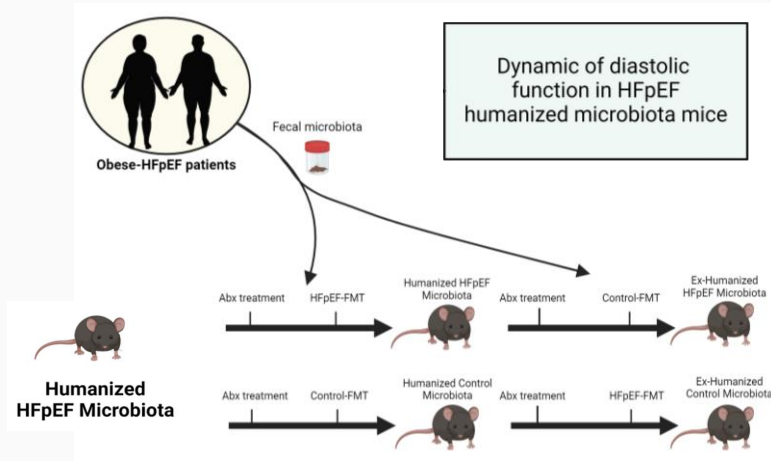
Heart



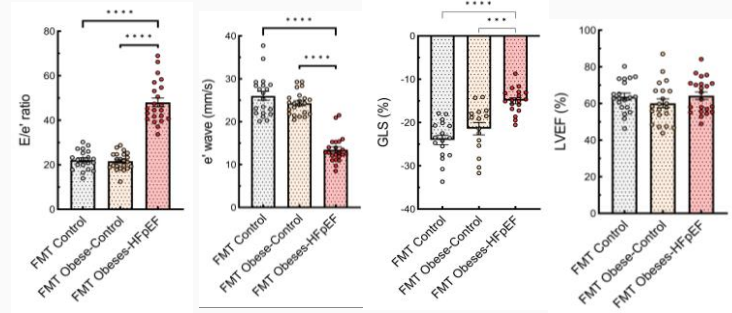
Top Downregulated ↓



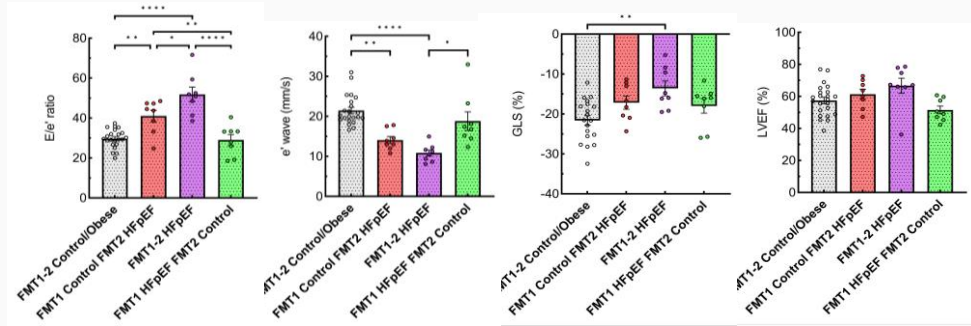
Does FMT from Healthy Individuals Improve Diastolic Function in HFpEF Humanized Microbiota Mice?



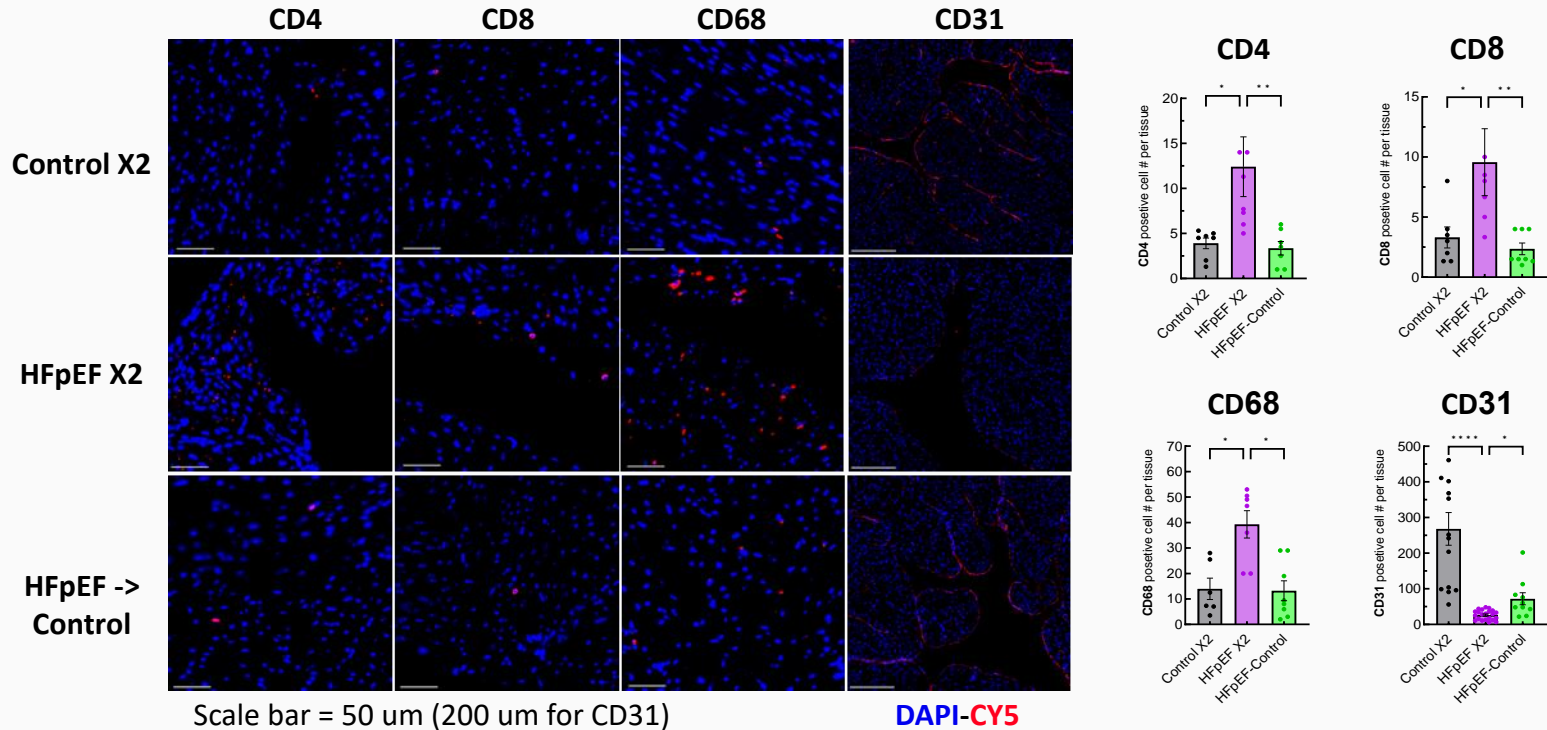
After FMT 1



After FMT 2



Improved Myocardial Inflammation and Endothelial Dysfunction after FMT from Control to Humanized Microbiota Mice



Conclusions

- We demonstrate a causative link between gut microbial dysbiosis and HFpEF progression
- Gut microbiota from obese HFpEF patients induces several proinflammatory and profibrotic signals, along with metabolic profile alterations, that could worsen HFpEF in mice
- Our study suggests that susceptibility to HFpEF may be transmissible in obese individuals and can potentially be modified through gut microbial manipulation as a therapeutic target



Acknowledgments

Research Team:

Cardiovascular Research Center:

Prof. Rabea Asleh, MD, PhD
Prof. Offer Amir, MD
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Noor Abu Salih - MSc student
Emily Peretz – BSc student
Kareem Abd Rabu – MSc
Hadeyah Mohsen – MSc student
Katy Srojy – MSc student



Collaborations:

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Faculty of Life Sciences, HU
Prof. Eran Elinav lab -
Weizmann institute
Prof. Yael Houry-Haddad -
Faculty of Dental Medicine
Prof. Rifaat Safadi lab -
The liver institute
Prof. Ronit Abramovich lab -
Wohl Institute



Funding (gut microbiome and HFpEF Project):

The Israel Science Foundation (ISF)



Thank You

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