Phenylketonuria (PKU)

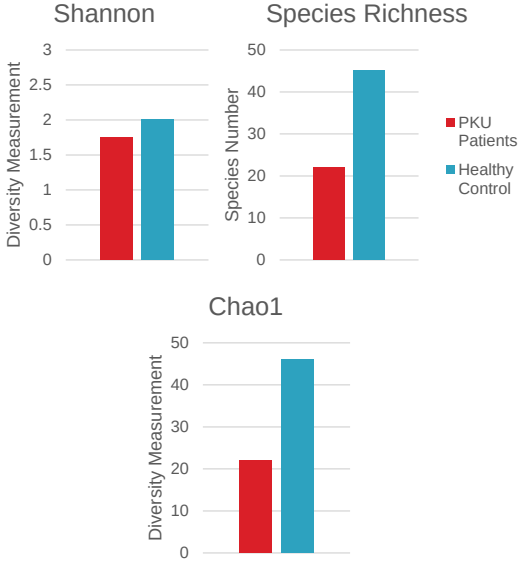
- Inability to metabolize phenylalanine
- Dietary management:
  - Reduced Phe intake
  - Low Phe/Phe-free medical foods

Rocha, MacDonald. Pediatric Health Med Ther. 2016;7:155-63.

13

PKU and the Microbiome (Pinheiro de Oliveira, 2016)

- Reduction in diversity and richness
- Structurally distinct
  - ↑ Bacteroidetes, Verrucomicrobia, ***Akkermansia***, *Lachnospiraceae*, *Peptostreptococcaceae*, *Prevotella*
  - ↓ ***Alistipes***, *Parabacteroidetes*, *Family XIII UCG-001*

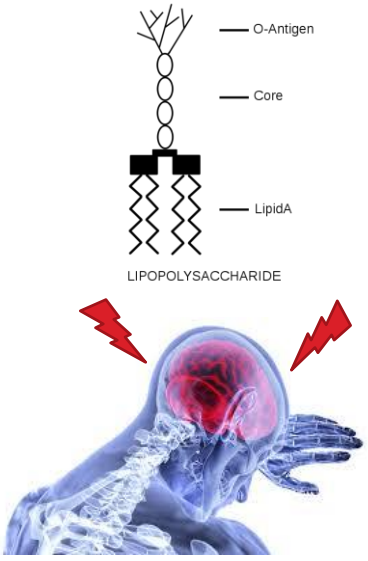


Pinheiro de Oliveira, et al. PLoS One. 2016;11(6):e0157513.

14

PKU and the Microbiome (Pinheiro de Oliveira, 2016)

- Functionally distinct microbiota
- Significant changes
  - ↑ **lipopolysaccharide biosynthesis proteins**, citrate cycle, …
  - ↓ **Glycolysis/Gluconeogenesis, starch and sucrose metabolism,** Phe, Tyr, Trp, Val, Leu, and Ile biosynthesis, …

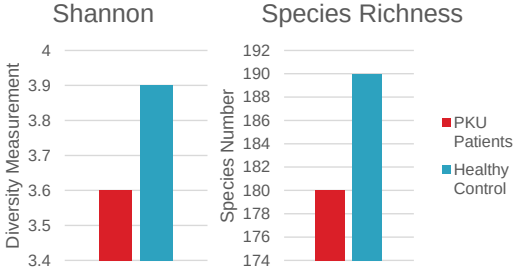


Pinheiro de Oliveira, et al. PLoS One. 2016;11(6):e0157513.

15

PKU and the Adult Microbiome (Mancilla, 2021)

- Trend in reduction of diversity and richness
- Structurally distinct
  - ↑ *Bifidobacterium*, *Bacillus*, **Alistipes**, *Clostridium*, ***Akkermansia***, *Bacteroides*
  - ↓ ***Faecalibacterium***, *Lactobacillus*, *Prophymonas*, *Blautia*, *Frisingicoccus*



Mancilla, et al. Microorganisms. 2021;9:530.

16

PKU and the Adult Microbiome (Mancilla, 2021)

- Functionally distinct microbiota
- Significant changes
  - ↑ Biotin biosynthesis II, Superpathway of N-acetylneuraminate degradation, Allantoin degradation to glyoxylate III, Gluconeogenesis
  - ↓ Creatine degradation II, Superpathway of 2,3-butanediol biosynthesis

Mancilla, et al. Microorganisms. 2021;9:530.

17

PKU Diet and the Microbiome (Bassanini, 2019)

- Focus on the effect of the PKU diet
- No changes in diversity detected
- Structurally distinct
  - ↑ *Lachnospiraceae*, *Blautia*, *Clostridium*
  - ↓ *Ruminococcacceae*, ***Faecalibacterium***, *Dialister*

Bassanini, et al. Front Cell Infect Microbiol. 2019;9:101.

18

PKU Diet and the Microbiome (Verduci, 2018)

- Focus on SCFAs and butyrate production
- No assessment of communal diversity or structure
- Looked at shifts in known butyrate-producing taxa
  - ↓ ***Faecalibacterium*** *prausnitzii, Roseburia* spp.

Verduci, et al. Nutr Metab Cardiovasc Dis. 2018;28(4):385-92.

19

Glycogen Storage Diseases (GSD)

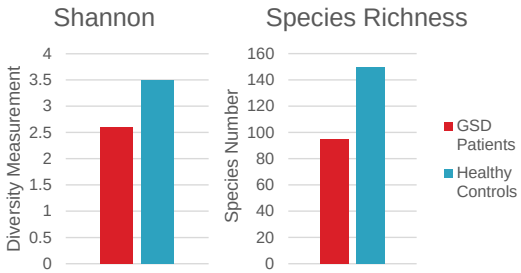
- Inability to metabolize glycogen (synthesis, metabolism)
- Dietary therapy
  - **Uncooked cornstarch**
  - Polyunsaturated fats to reduce hyperlipidemia

1. Heller, et al. J Pediatr Gastroenterol Nutr. 2008;47 Suppl 1:S15-21. **2.** Bali, et al. Glycogen Storage Disease Type I. GeneReviews® [Internet]. 2006.

20

GSD and the Microbiome (Colonetti, 2019)

- Reduced species richness and Shannon diversity
- Structurally distinct
  - Presence/absence significant
  - ↑ Actinobacteria, Proteobacteria, *Escherchia/Shigella, Lactobacillus*
  - ↓ Euryarchaeota, *Coprococcus*, *Blautia*, *Anaerostipes*, *Odoribacter*, ***Faecalibacterium***



** All GSD patients in study were on uncooked cornstarch

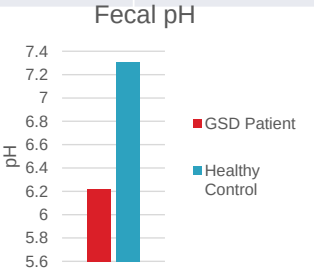
Colonetti, et al. PLoS One. 2019;14(4):e0214582.

21

GSD and the Microbiome (Colonetti, 2019)

- Trends mirror inflammatory bowel disease (IBD) and cirrhosis
  - Diet-induced dysbiosis is clear
  - Does GSD alone induce dysbiosis??
- GSD patients on uncooked cornstarch had:
  - ↓ fecal pH
  - ↑ fecal carbohydrates

GSD	NAFLD Overlap
↑ Actino/Proteobacteria, *Escherchia/Shigella, Lactobacillus*	↑ *Lactobacillus*
↓ Euryarchaeota, *Coprococcus, Blautia, Anaerostipes, Odoribacter, Faecalibacterium*	↓ *Coprococcus, Blautia, Anaerostipes, Faecalibacterium*



1. Colonetti, et al. PLoS One. 2019;14(4):e0214582. **2.** Da Silva, et al. Sci Rep. 2018;8:144.

22

Diet… What is the Effect in General?

- Diet plays a huge role in shaping gut microbiota naturally
- What impact does specialized diet play in the previous data?
- How do we study the disease effect independent of diet?
  - It is important to understand both simultaneously

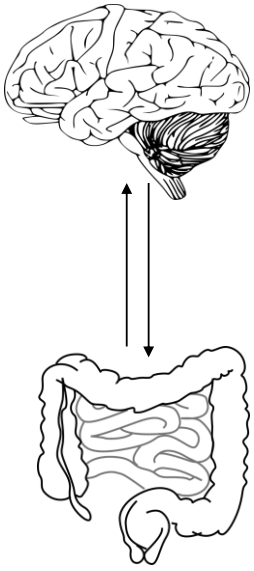
23

The Gut-Brain Axis and the Impact of Dysbiosis on IEM Disease Presentation

24

The Gut-Brain Axis

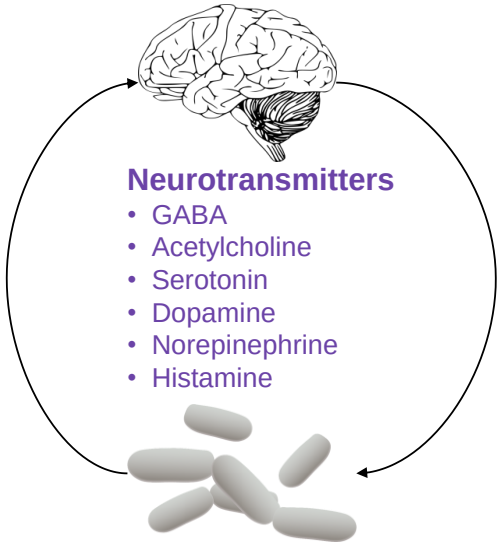
- A bidirectional communication pathway between the gut and the CNS
  - Traditionally viewed in terms of neurotransmitters
  - Uses other traditional physiological systems to operate
    - Endocrine system
    - Immune system



25

Host-Microbe Neurotransmitter Interactions

Producing bacteria
- Dopamine
  - *Bacillus subtilis*
  - *Staphylococcus aureus*
- Serotonin
  - *Klebsiella pneumoniae*
  - *Lactobacillus plantarum*
- Acetylcholine
  - *Lactobacillus plantarum*
- GABA
  - *Lactobacillus*
  - *Bifidobacterium*
  - *Escherichia coli*

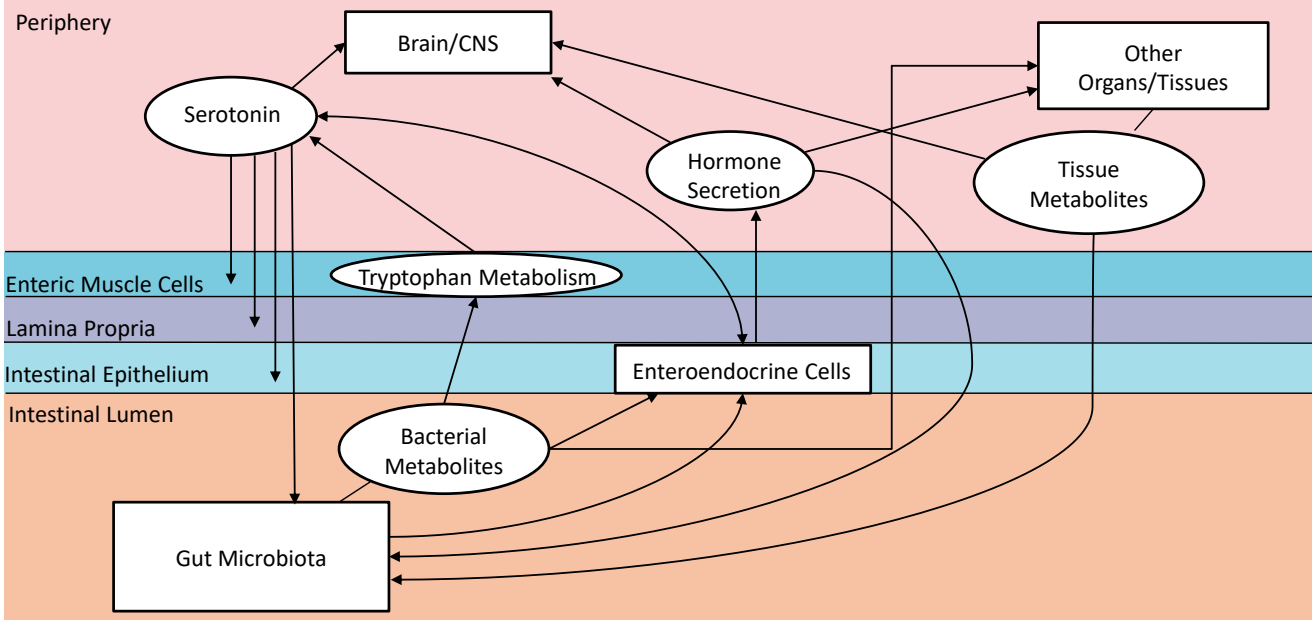


Consuming bacteria
- Dopamine
  - *Escherichia coli* O157:H7 (EHEC)
  - *Pseudomonas aeruginosa*
- Serotonin
  - *Klebsiella pneumoniae*
  - *Lactobacillus plantarum*
- GABA
  - *Escherichia coli*

Strandwitz. Brain Res. 2018;1693:128-33.

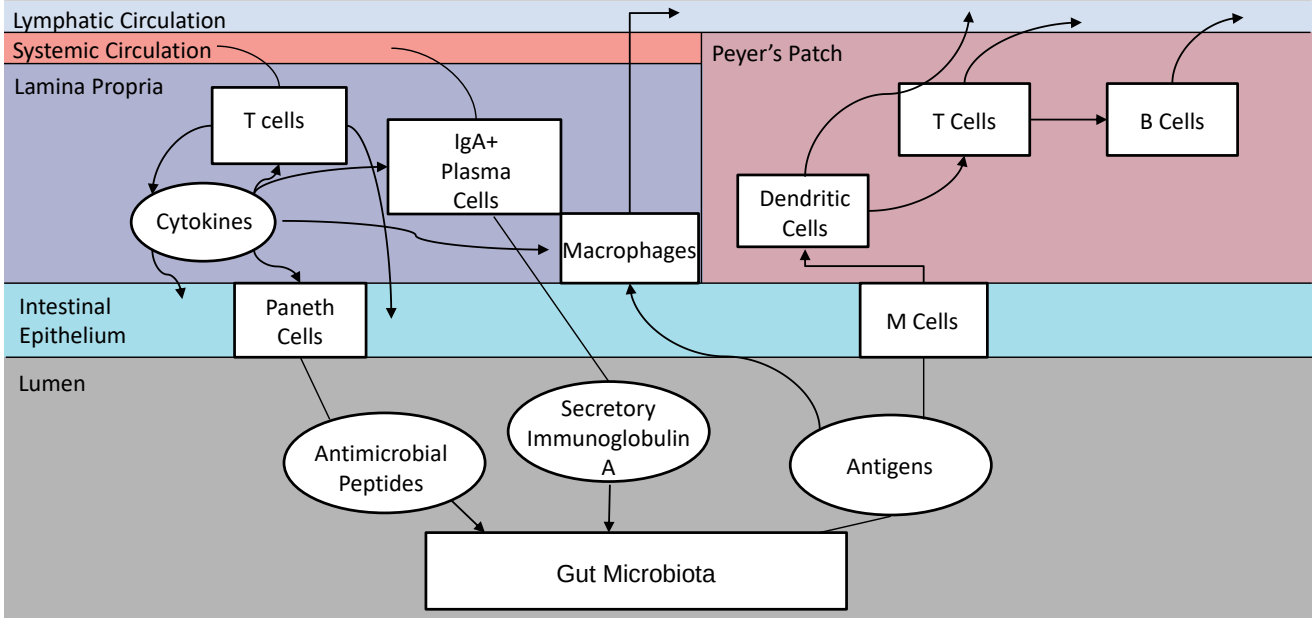
26

Host-Microbe Endocrine Interactions



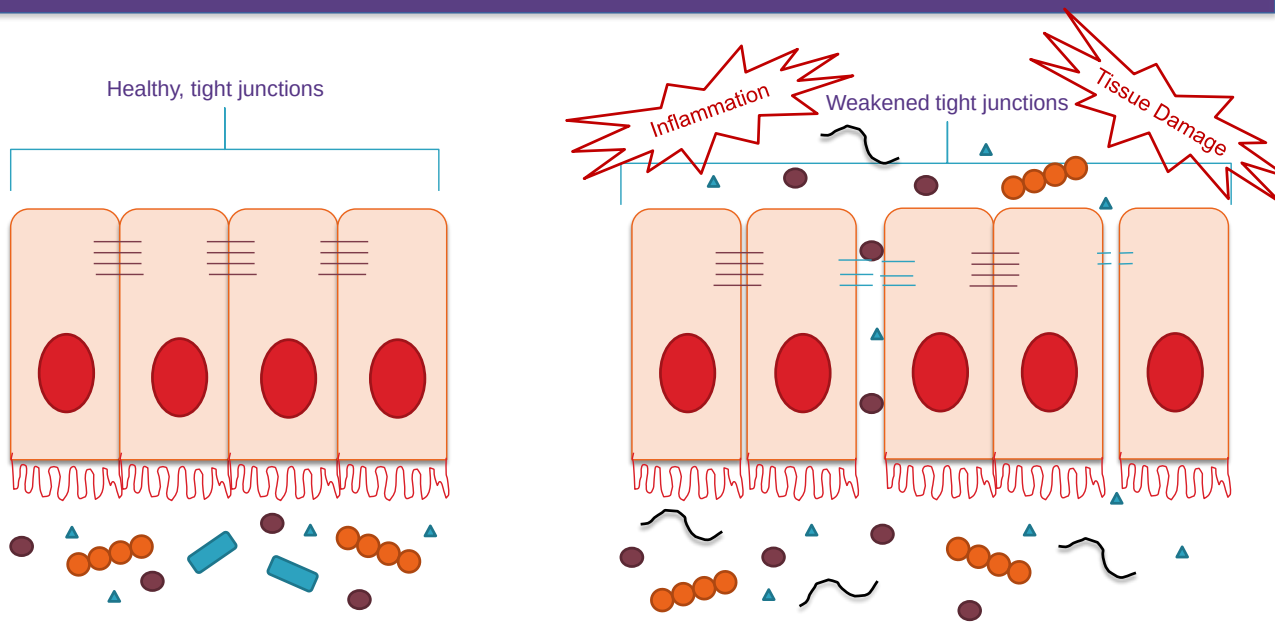
27

Host-Microbe Immune Interactions



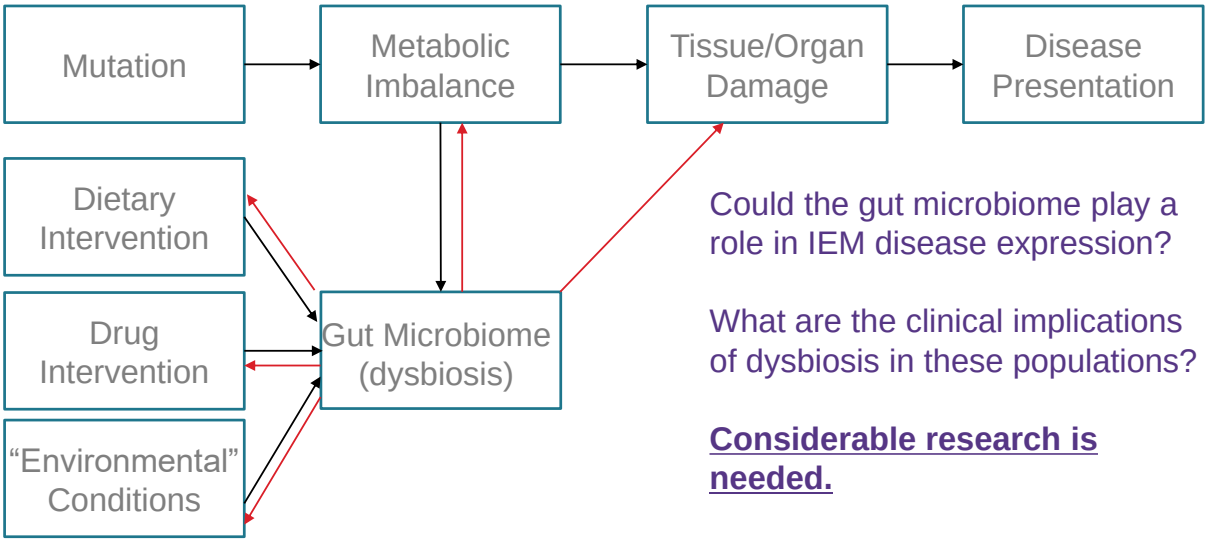
28

Dysbiosis and Leaky Gut



29

Impact of Dysbiosis on IEM Clinical Presentation



Could the gut microbiome play a role in IEM disease expression?

What are the clinical implications of dysbiosis in these populations?

Considerable research is needed.

30

Pre-, Pro-, and Synbiotics in IEMs

31

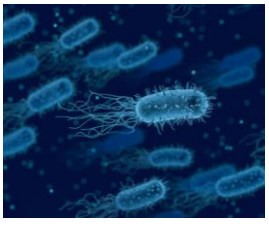
What are Pre-, Pro-, and Synbiotics?

Prebiotics

Substrates that are selectively utilized by host microorganisms, conferring a health benefit[1]

- Primarily oligosaccharide carbohydrates
  - Asparagus, garlic, onion, wheat, banana, rye, peas, …

Probiotics



Live microorganisms which when administered in adequate amounts confer a health benefit on the host[2]

- Which one depends on benefit of interest
  - *Lactobacillus rhamnosus GG* for diarrhea
  - *Saccharomyces boulardii* for adjunct treatment of *Helicobacter pylori*

Synbiotics

- Combination of pre-/probiotics together
  - Enhances probiotic and resident microbiota[3]
- Can be targeted:
  - Loaded with fructans plus lactic acid bacteria
  - Loaded with glucose derived oligosaccharides plus *Ruminococcus*
- Can decrease undesirable metabolite concentrations

1. Gibson, et al. Nat Rev Gastroenterol Hepatol. 2017;14(8):491-502. **2.** Hill, et al. Nat Rev Gastroenterol Hepatol. 2014;11(8):506-14. **3.** Bengmark. Gastroenterol Clin North Am. 2005;34(3):413-36.

32

Do They Work for Disease - IBD?

	Efficacious	Non-Efficacious	Citations
Prebiotics	Fructans	–	Marushko, et al. Modern Pediatrics. 2013:66-72.
Probiotics	*Lactobacillus spp.*, *Enterococcus faecium*, *Saccharomyces boulardii*	*Lactobacillus acidophilus La-5* and *Bifidobacterium animalis* subsp. lactis BB-12	Tomasello, et al. J Biol Regul Homeost Agents, 2015;29(2):265-72. Wildt, et al. J Crohns Colitis. 2011;5(2):115-21.
Synbiotics	*Bifidobacterium longum* and Synergy 1 (Raftilose®)	–	Steed, et al. Aliment Pharmacol Ther. 2010;32(7):872-83.

- Recall… IBD is common in GSD

33

Do They Work for IEMs?

- Not much data for IEMs…

IEM	Type	Efficacy?	Citations
PKU	Probiotic - pHENOMMenal	Yes in mouse model	Durrer, et al. PLoS One. 2017;12(5):e0176286.
Trimethylaminuria	Probiotic - *Methanomassiliicoccus luminyensis B10*	Theoretical prediction	Brugère, et al. Gut Microbes. 2014;5(1):5-10.
Hyperoxaluria	Probiotics – *Bifidobacterium animalis* subsp. lactis	Yes in mouse model	Klimesova, et al. Urolithiasis. 2015;43(2):107-17.
	Oxalobacter formigenes		Hatch, et al. Am J Physiol Gastrointest Liver Physiol. 2011;300(3):G461-9.
	Synbiotics - Oxadrop® and Agri-King Synbiotic	No in patients	Lieske, et al. Kidney Int. 2010;78(11):1178-85.

34

Theoretically, What Can We Do About Dysbiosis?

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Surveillance

Monitoring patient microbiota

Dietary Supplementation

Leveraging diet strategically

Experimental Technologies

Continued research into novel technologies

35

Microbiome Surveillance

NLC NUTRICIA LEARNING CENTER

- What if we tracked a patient's gut microbiome as disease progresses?
  - I do this for Succinic Semialdehyde Dehydrogenase Deficiency
    - IEM of GABA metabolism
- Far from being a clinical service right now…

36

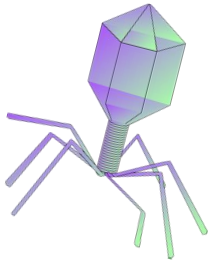
Dietary Supplementation

- Preemptive strategies
  - Encourage breastfeeding if possible
  - Diversify patient's diet within dietary restrictions
    - Particularly foods containing fiber
  - Choose formulas and medical foods with prebiotics
- Proactive strategies
  - Directed pre/pro/synbiotics targeting "reduced" taxa
  - Recommending lifestyle changes to promote healthy microbiota

37

Experimental Technologies

- Bacteriophage Technology
  - Viruses that attack certain bacteria only
  - Creating smart "phage cocktails" could allow for tailored changes to the microbiome structure
- Fecal Transplantation
  - Using stool from a healthy donor to reseed a healthy gut community
  - Last ditch effort to start the gut microbiome
- Transgenic probiotics
  - Leverage microbial metabolism strategically



38

Conclusions

1. Gut microbiome is essential for healthy physiology.
2. IEMs may be associated with dysbiosis.
3. Dysbiosis may be a pathogenic factor in IEMs that should be considered.
4. Modulating the gut microbiome may be a tool to mitigate IEM severity.

39

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MAYO CLINIC
CLIR - Collaborative Laboratory Integrated Reports

ssadh
Succinic Semialdehyde Dehydrogenase Deficiency Association

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40

Thank you!

To obtain a certificate of attendance for 1 CE hour, please complete a brief survey which you can access via the QR code below or the following link: https://www.surveymonkey.com/r/Dysbiosis_IEM

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41