

Impact of the Gut Microbiome on Obesity

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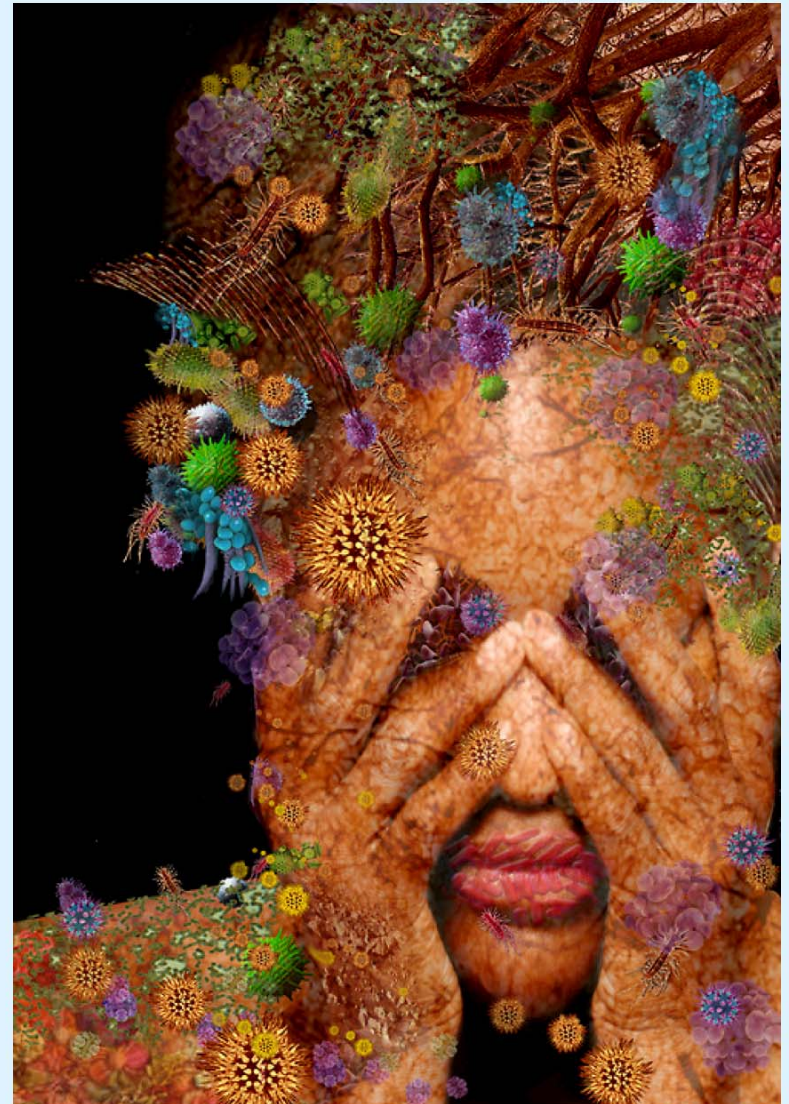
Humans are home to trillions of microbes

Fun facts:

- Trillions of microbial cells (***microbiota***)
- 100X more microbial genes than human genes (***microbiome***)
- 50% of feces by weight; 10^{12} cells/g
- ~12 dominant taxa in the gut
- High inter-individual variation

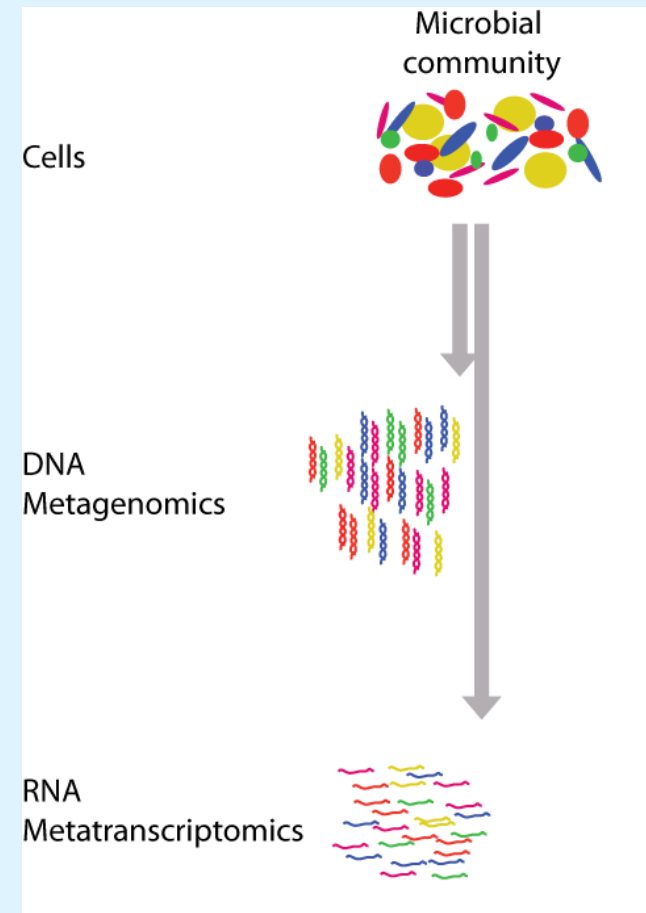
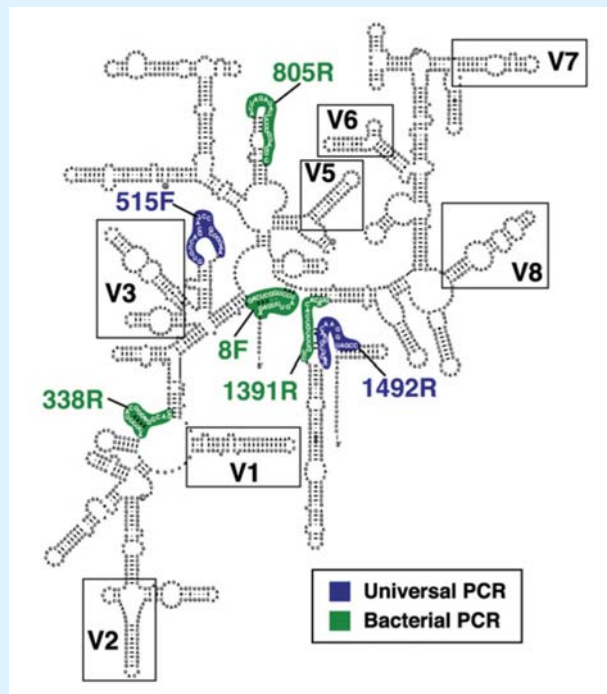
What do they do?

- Develop the immune system
- Protect us from pathogens
- Make essential vitamins and amino acids
- Alter drug outcomes
- ***Metabolize our diet***



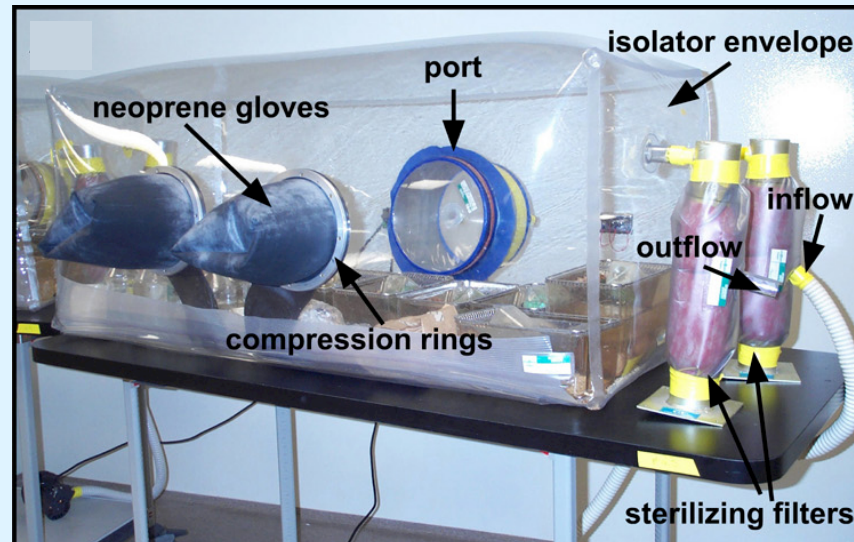
Key method #1: metagenomics

- 16S rRNA gene present in all Bacteria and Archaea
- Contains both fast- and slowly evolving regions
- Most 16S rRNA sequences come from uncultured, uncharacterized microbes



Key method #2: gnotobiotics

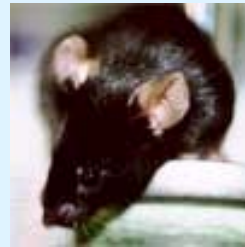
The stage:
A gnotobiotic isolator



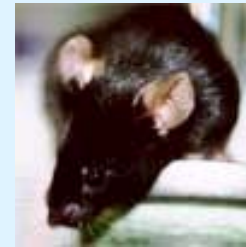
The players:



Germ-free



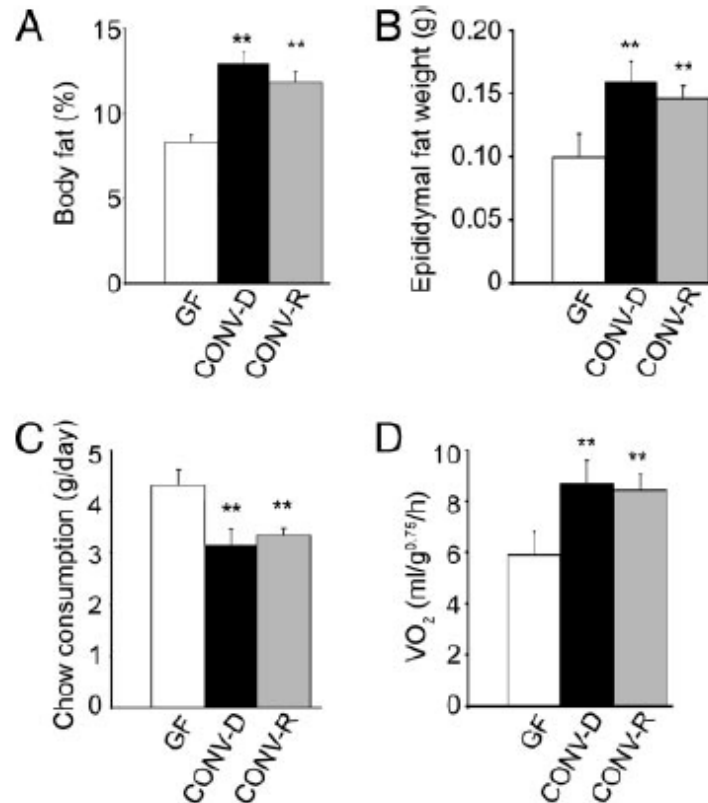
CONV-R
Conventionally
raised



CONV-D
Conventionalized or
mono-associated

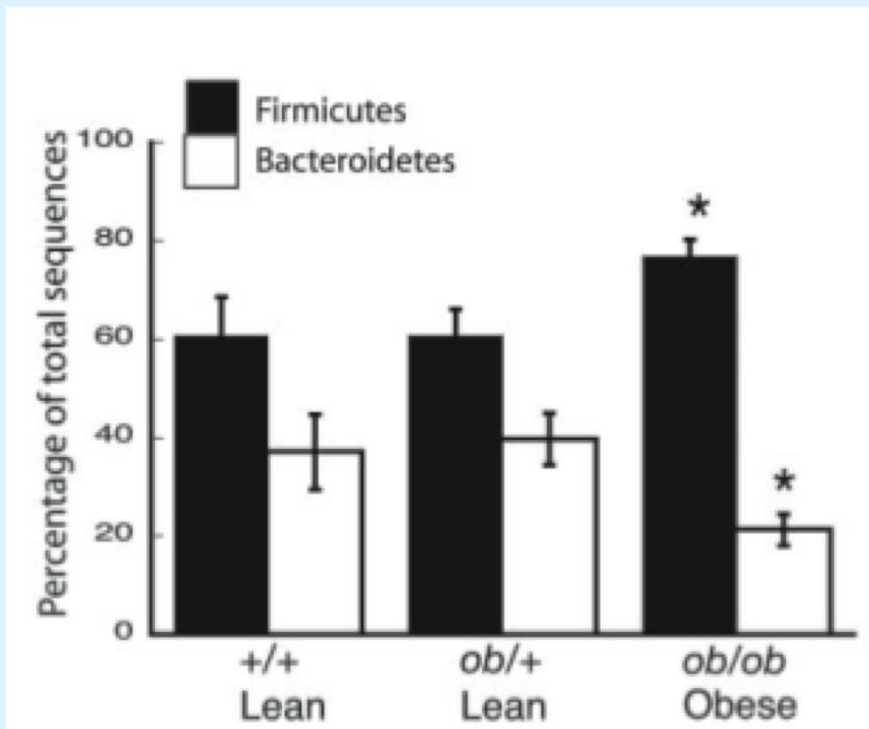
Gut microbes contribute to host adiposity

Colonization increases adiposity



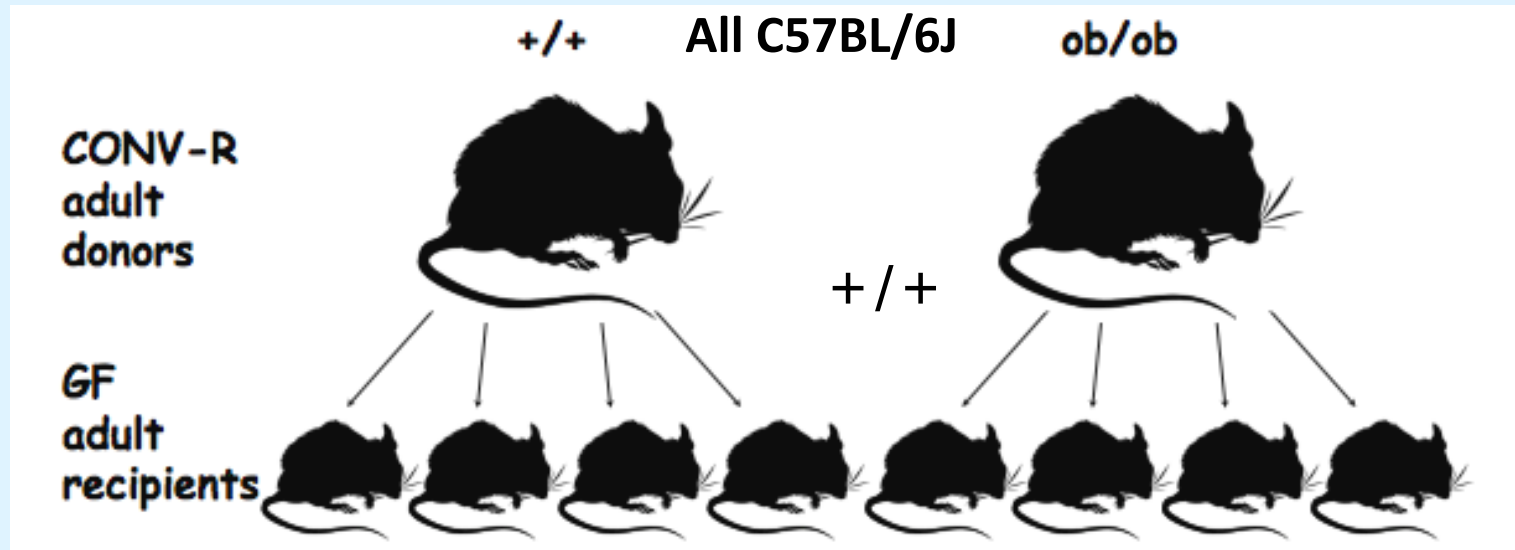
- Males and females have equivalent responses
- Observed in multiple genetic backgrounds
- Decreased chow consumption and increased metabolic rate

Obese mice have a distinct gut microbiota

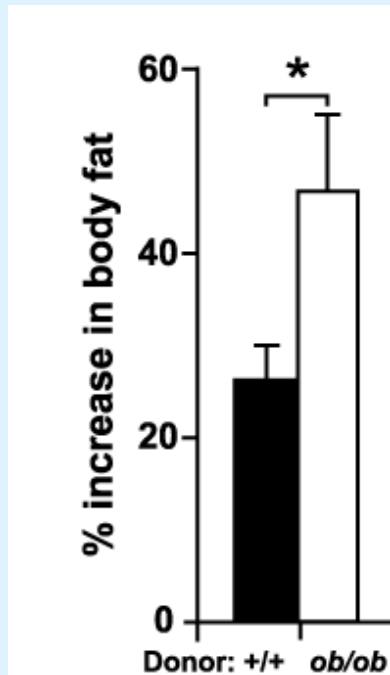


***ob/ob* mice – genetically induced obesity due to the lack of leptin (regulates satiety)**

“Microbiota transplantation”



Microbial transmission of adiposity



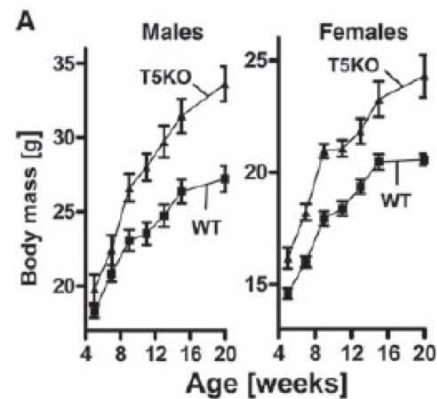
■ Mice colonized with a microbiota from a lean donor

□ Mice colonized with a microbiota from an obese donor

No significant difference in chow consumption, initial body fat, or initial weight

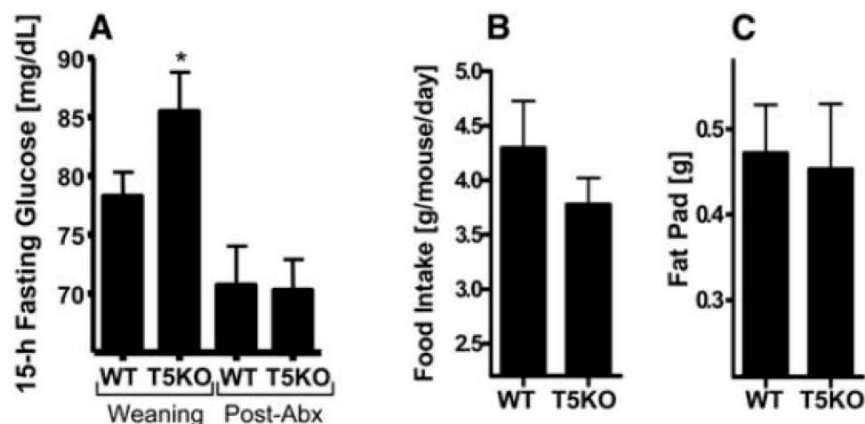
Metabolic syndrome in mice lacking TLR5

- Created mice null for Toll-like receptor 5, part of the innate immune system, expressed in the gut mucosa
- Found hallmark features of metabolic syndrome

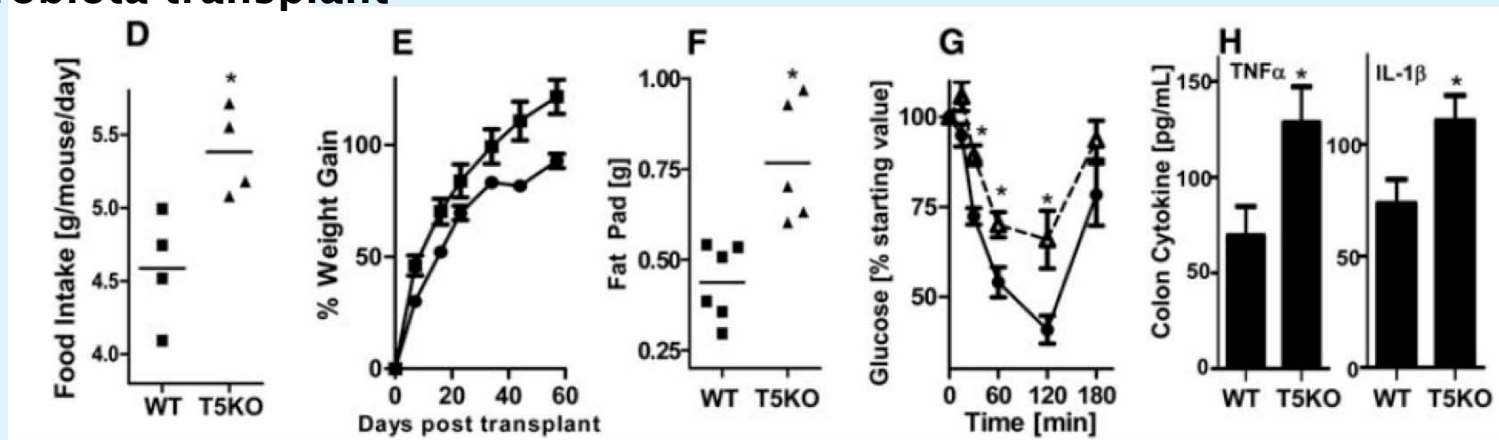


Metabolic syndrome depends on the gut microbiota

Antibiotics



Microbiota transplant



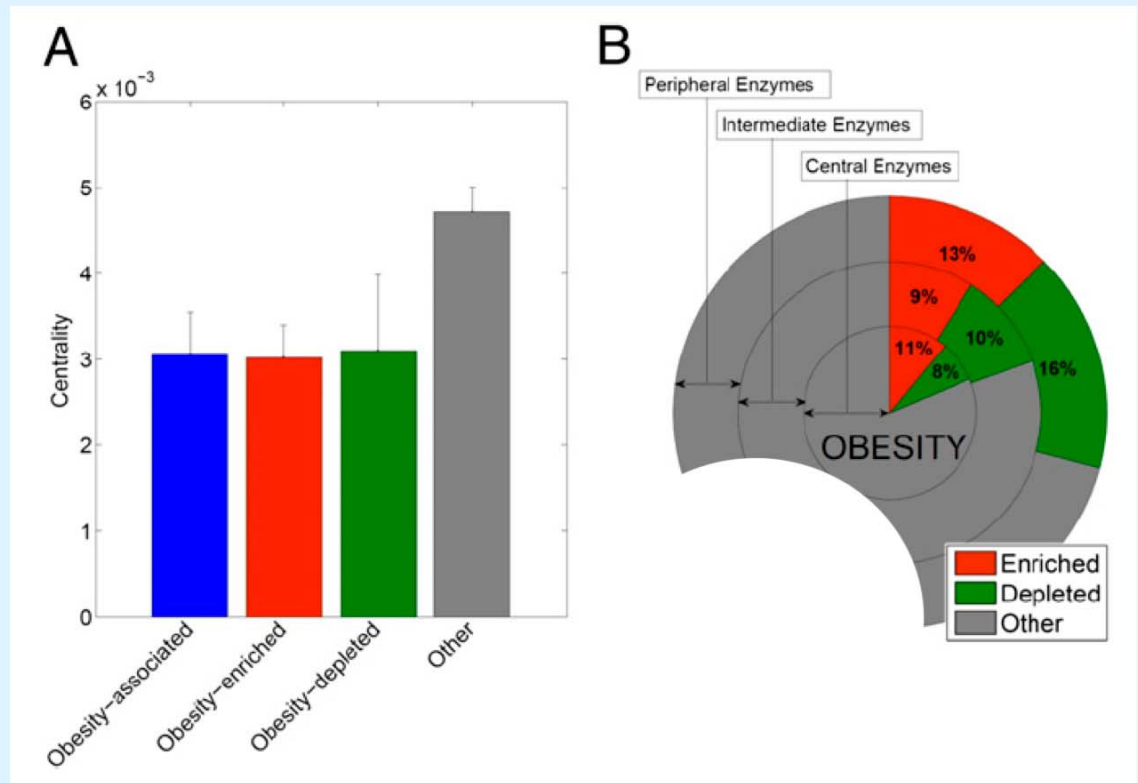
Obese and lean twins

- Monozygotic and dizygotic twin pairs with their mothers => 154 individuals sampled at 2 timepoints
- Relatives shared similar community structure and gene content
- No abundant shared bacterial species but extensive core set of genes
- > 300 microbial genes significantly associated with obesity

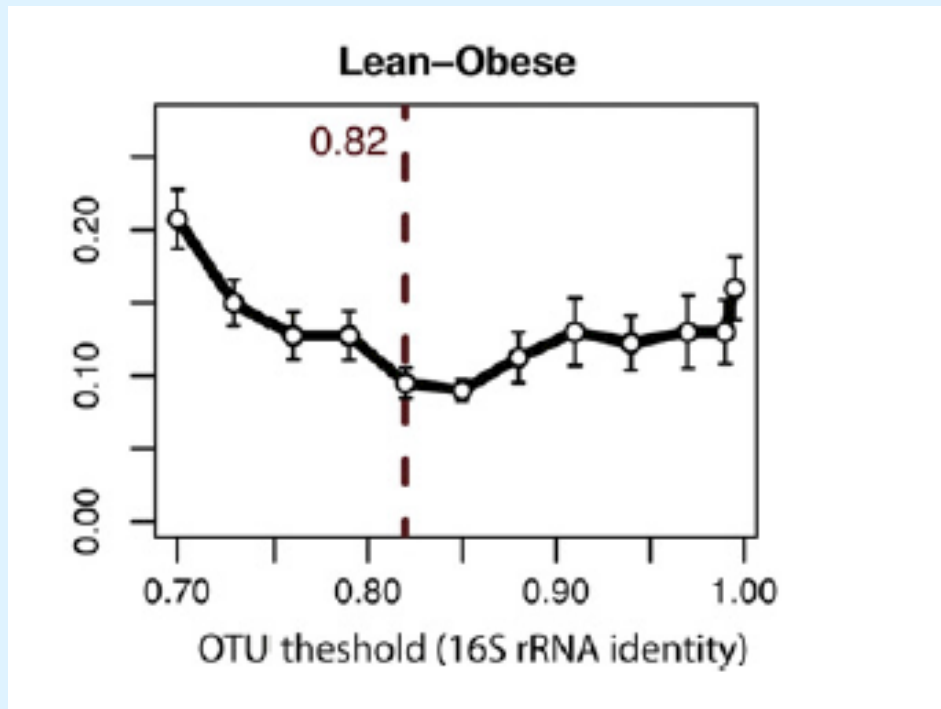


Network-wide differences between the obese and lean gut microbiome

- Metagenomic data – *in silico* metabolic network reconstructions
- 99 lean, overweight, and obese individuals
- 6 MZ lean or obese twin pairs and their mothers
- Gene-level and network-level differences between lean and obese microbiomes
- Differences tend to be at periphery of the network
- ***Obesity-associated genes are involved in carbohydrate transport, nitrate reduction, and xenobiotic metabolism***



The gut microbiota predicts BMI



90% accuracy using
discriminatory
bacteria identified
by machine
learning

**Diet, pregnancy, and antibiotics
re-shape the gut microbiome,
stimulating adiposity**

A century-old hypothesis

Arthur I. Kendall

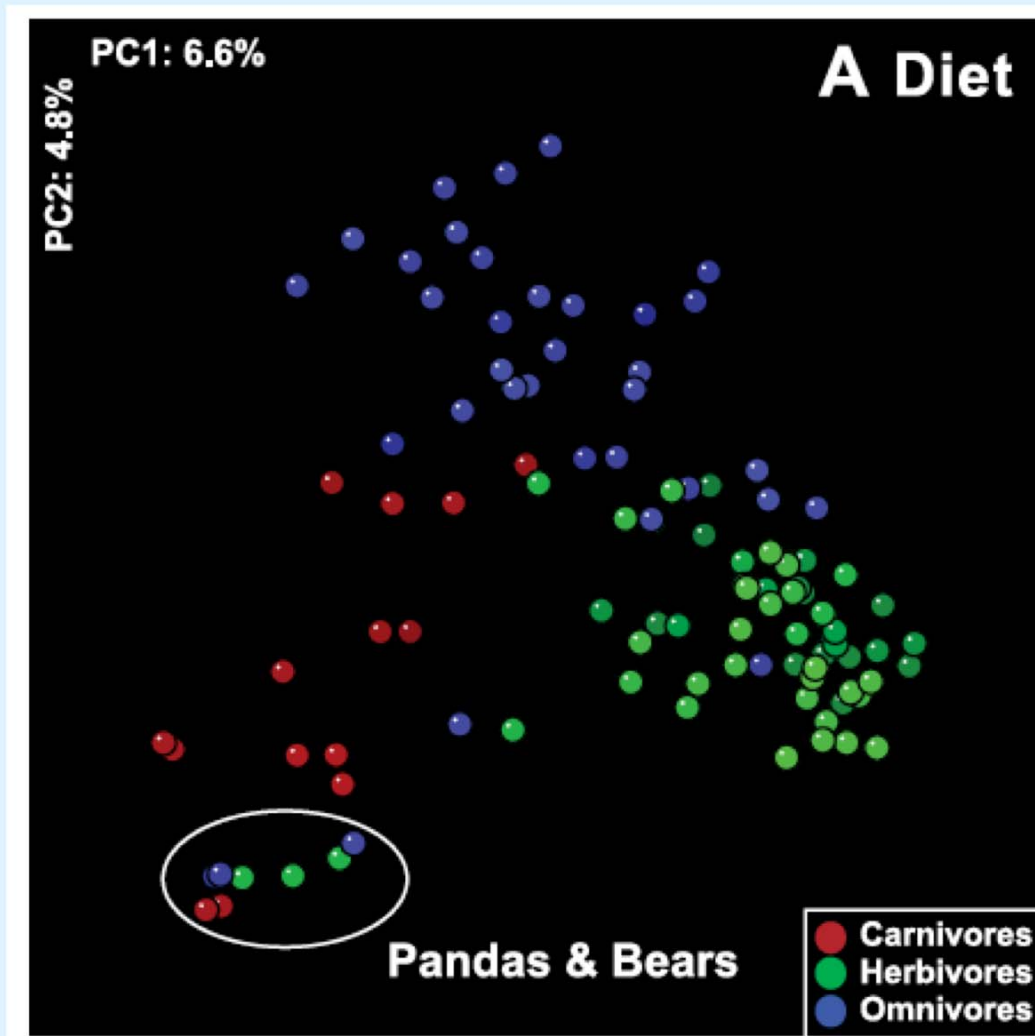
SOME OBSERVATIONS ON THE STUDY OF THE INTESTINAL BACTERIA

J. Biol. Chem. 1909 6: 499–507.

- As this food passes through the alimentary canal...at different levels of the tract it is decomposed in part by various types of bacteria. ***The predominating types of bacteria which take part in the decomposition are determined largely by the nature of the diet.***
- ...there is a parallelism between the nature of the diet and the character of the bacterial types represented in the intestinal and fecal flora.
- Hitherto this correlation between diet, intestinal flora and end products has been largely overlooked...

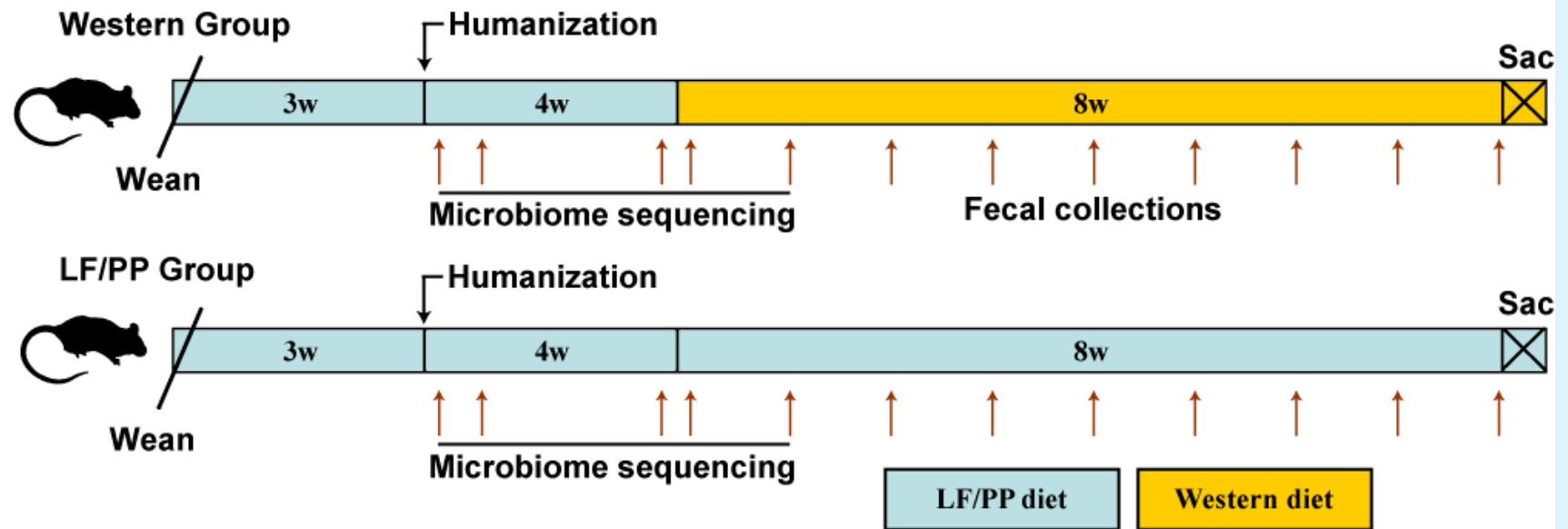


Long-term diet is associated with the gut microbiota



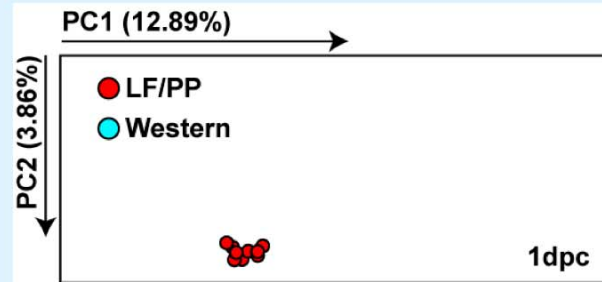
- Humans + 59 other mammals
- 2 zoos and the wild
- ***Carnivores are enriched for amino acid catabolism genes***

Diet rapidly alters the mouse gut microbiota

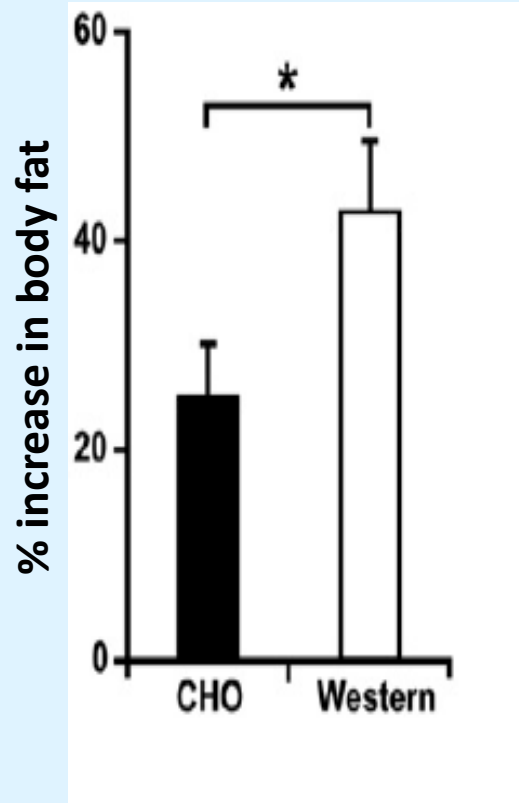


LF/PP=low-fat, plant polysaccharide-rich diet
Turnbaugh et al. Sci Transl Med. 2009;DOI: 10.1126/scitranslmed.3000322

Diet rapidly alters the mouse gut microbiota



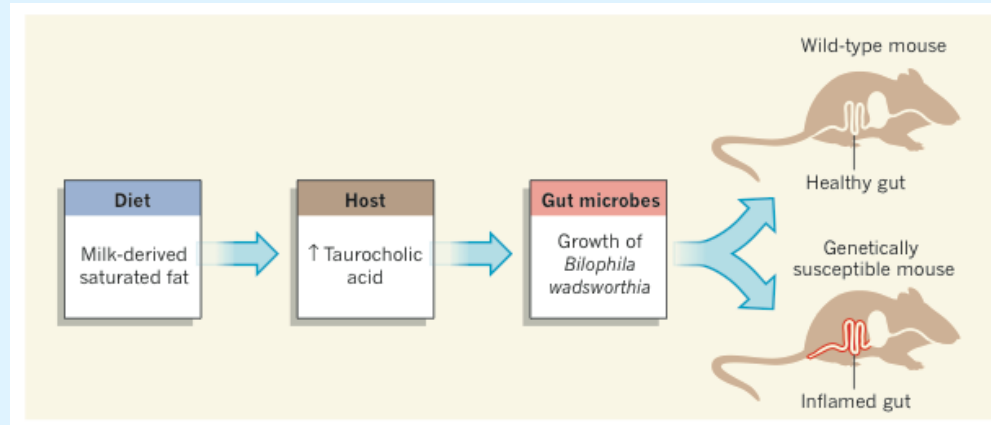
Microbial transmission of adiposity



- Mice colonized with a microbiota from a lean donor
- Mice colonized with a microbiota from an obese donor

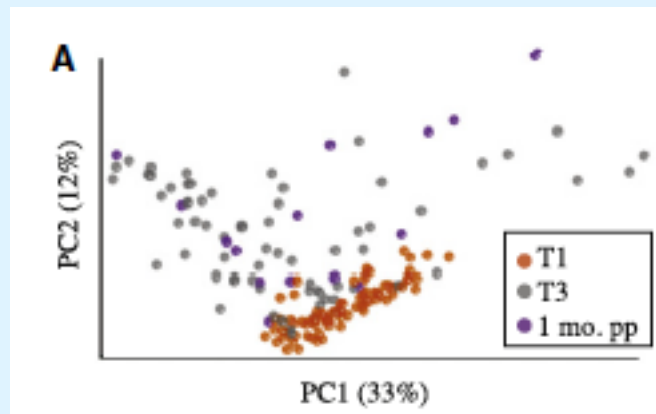
No significant difference in chow consumption, initial body fat, or initial weight

High-fat diets can also contribute to IBD

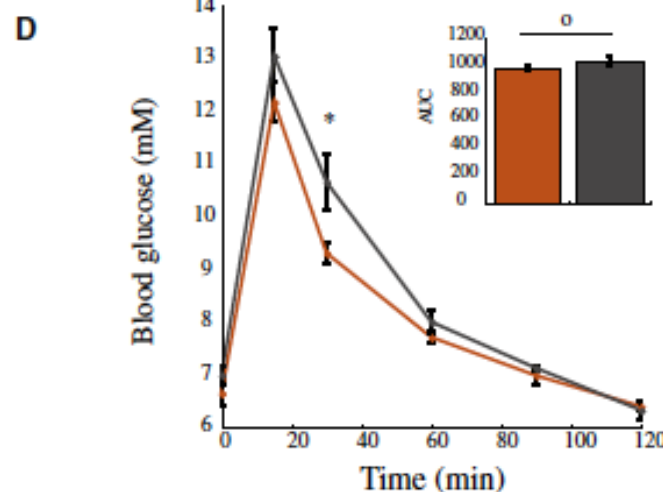
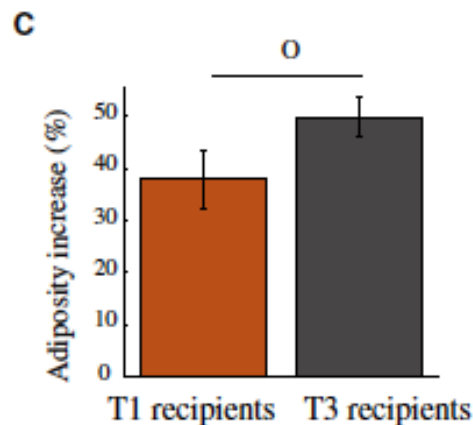


**Consumption of a high-fat diet increases *Bilophila*,
contributing to IBD in mice**

Pregnancy shifts the gut microbiota, promoting host adiposity

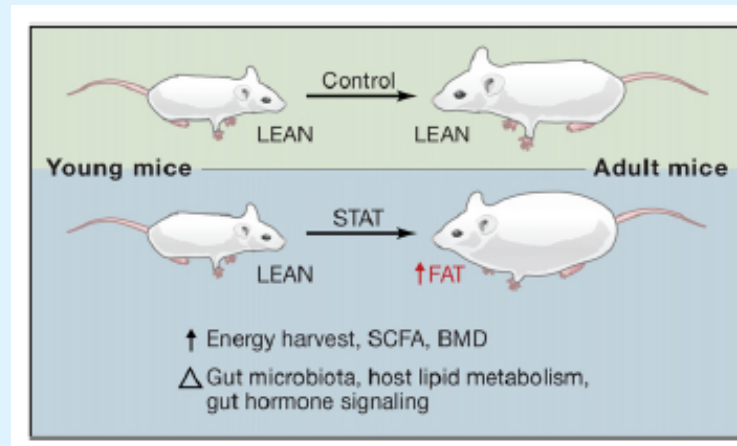
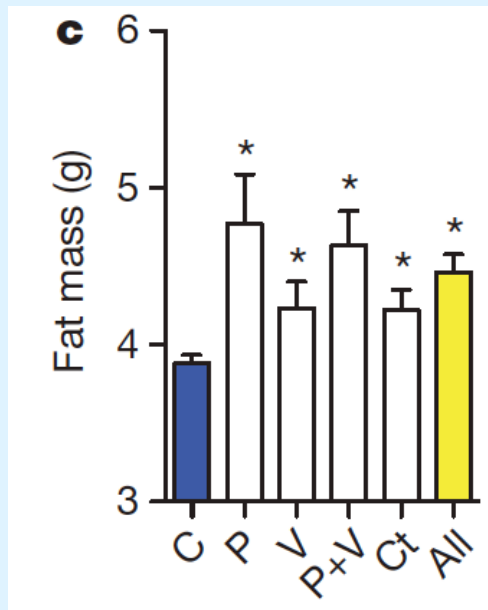


Shift in microbial community structure in 3rd trimester



Fecal transplantation to germ-free mice results in increased adiposity and blood glucose

Low dose antibiotics stimulate adiposity



Liou and Turnbaugh. Cell Metabolism.2012;16:408-10.
Cho et al. Nature 2012;488:621-6.

Mechanistic considerations

Gut microbes contribute to energy harvest

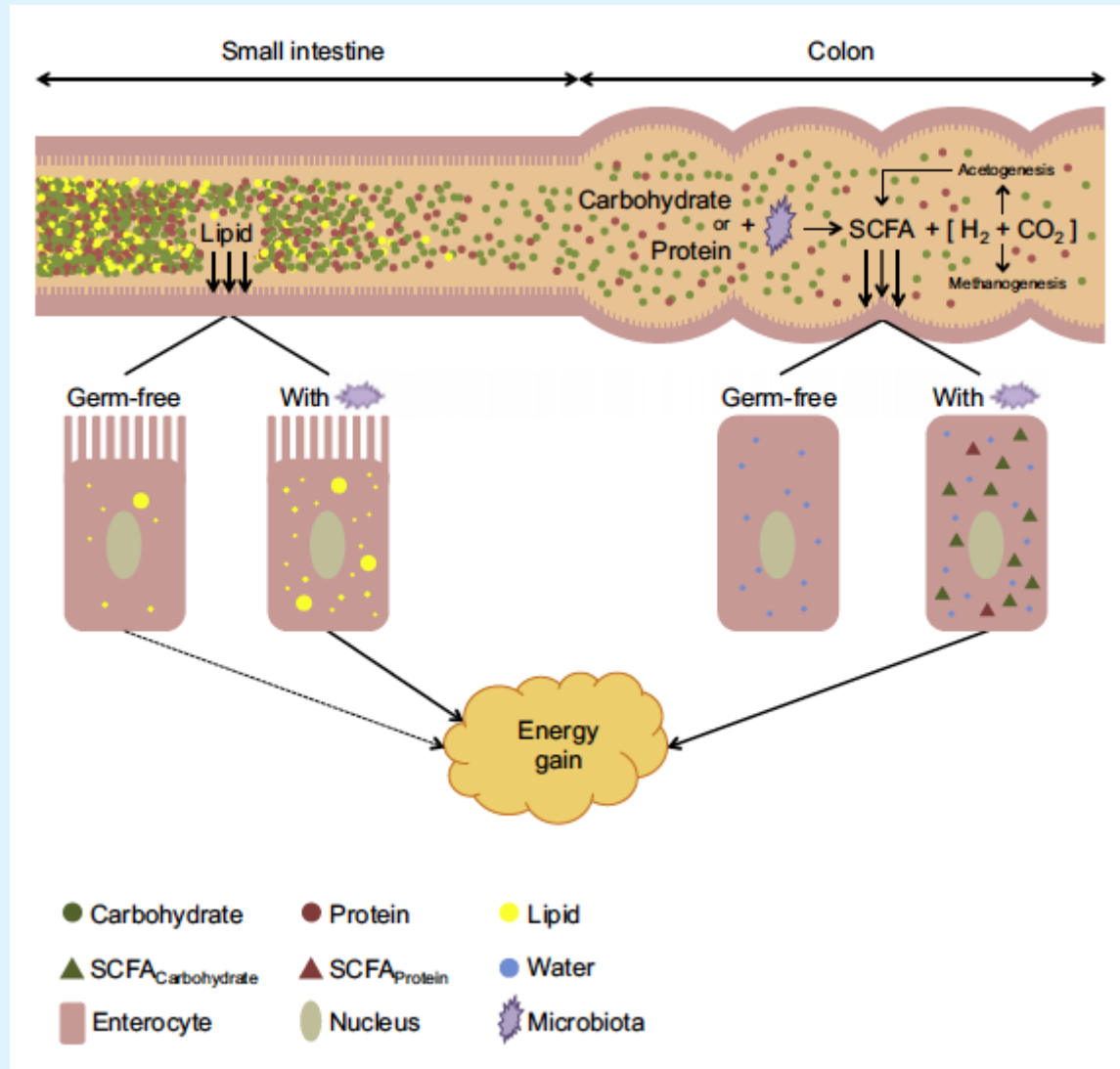
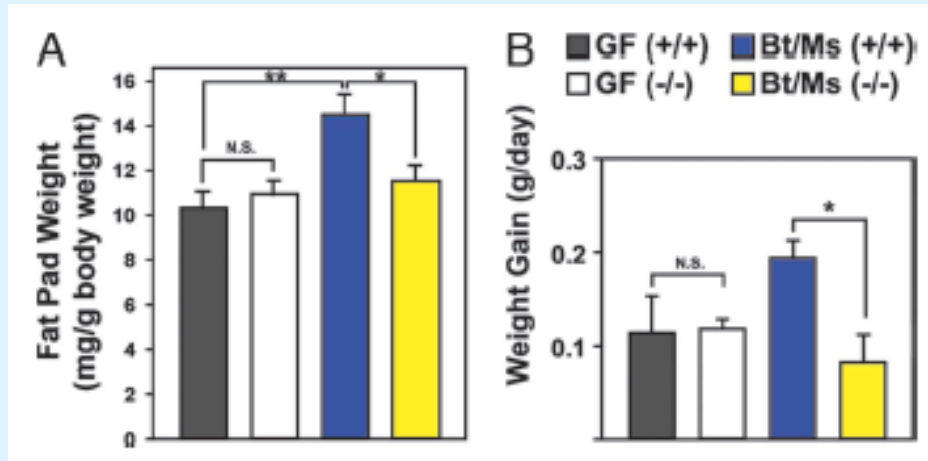
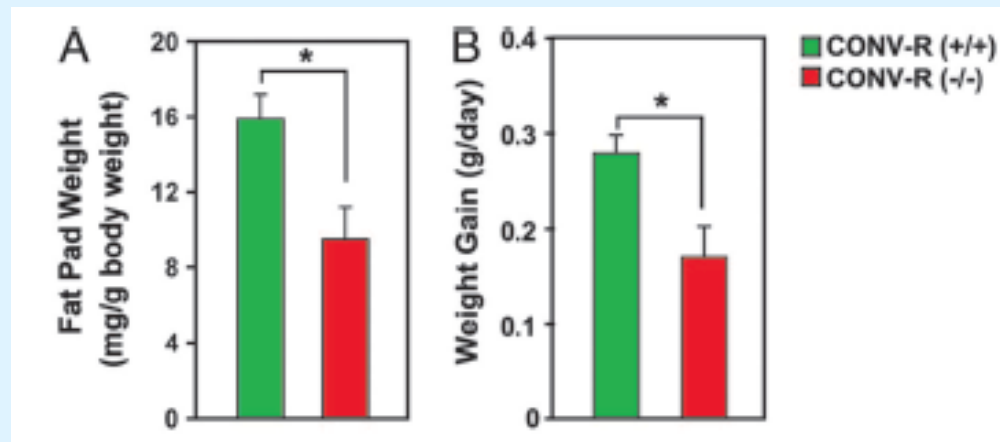


Figure from Carmody and Turnbaugh. *Cell Host Microbe*. 2012;12:259-61.
Semova et al., *Cell Host Microbe*. 2012;12:277-88.

Microbial SCFA signaling

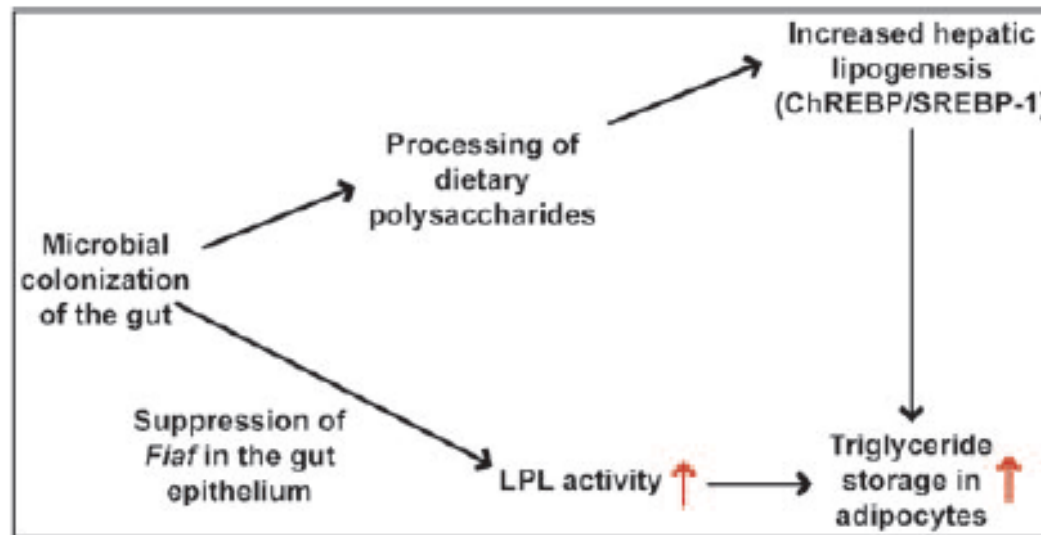
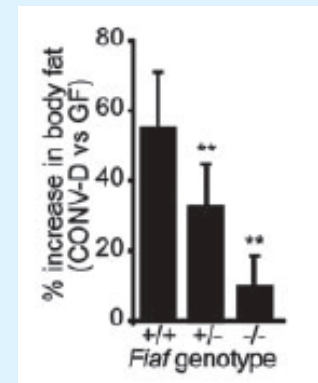
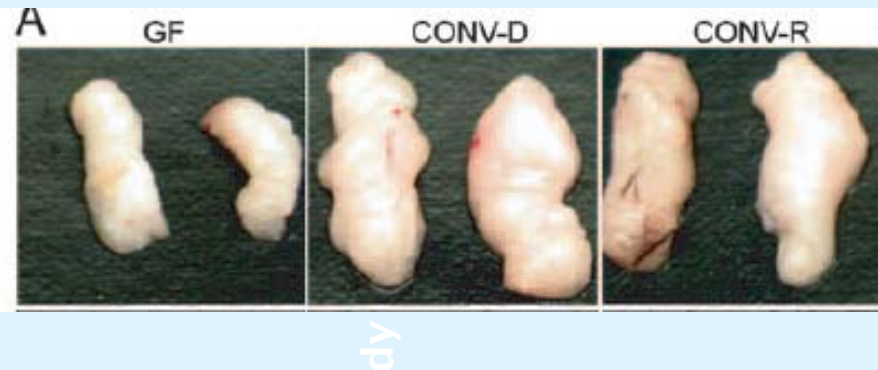


Bi-association
requires GPR41 to
increase weight/
adiposity

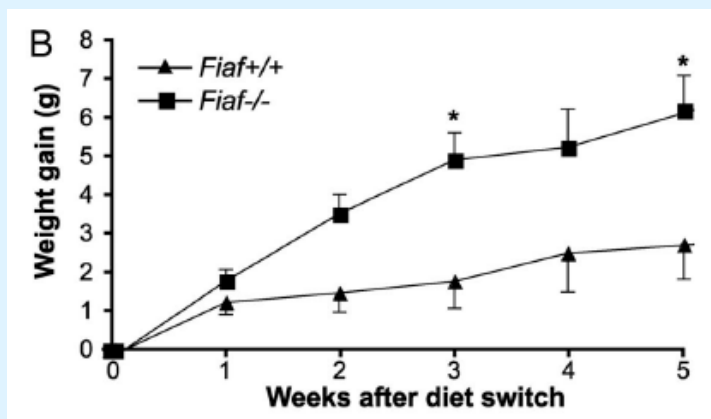
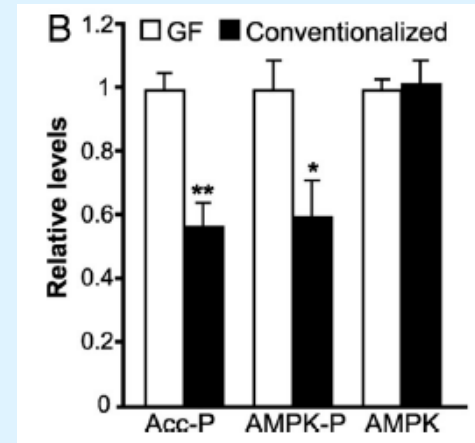
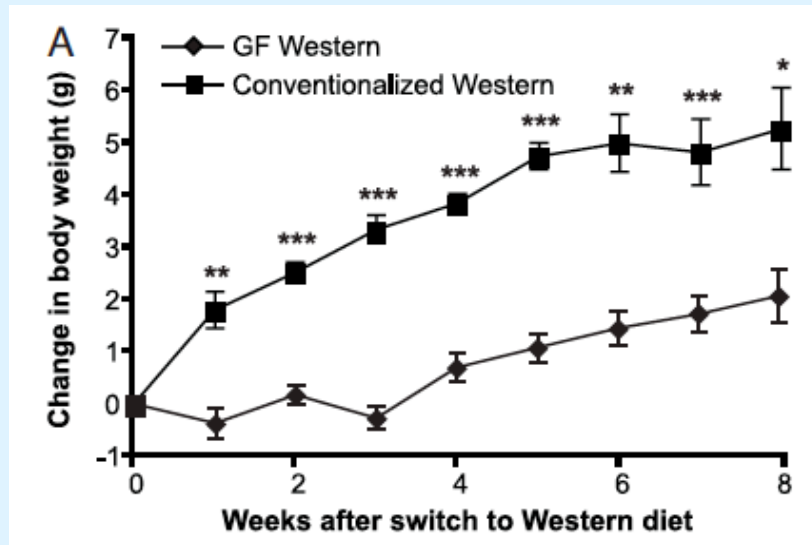


Conventionalization
has a blunted effect
in GPR41 KOs

Colonization suppresses gut *Fiaf*

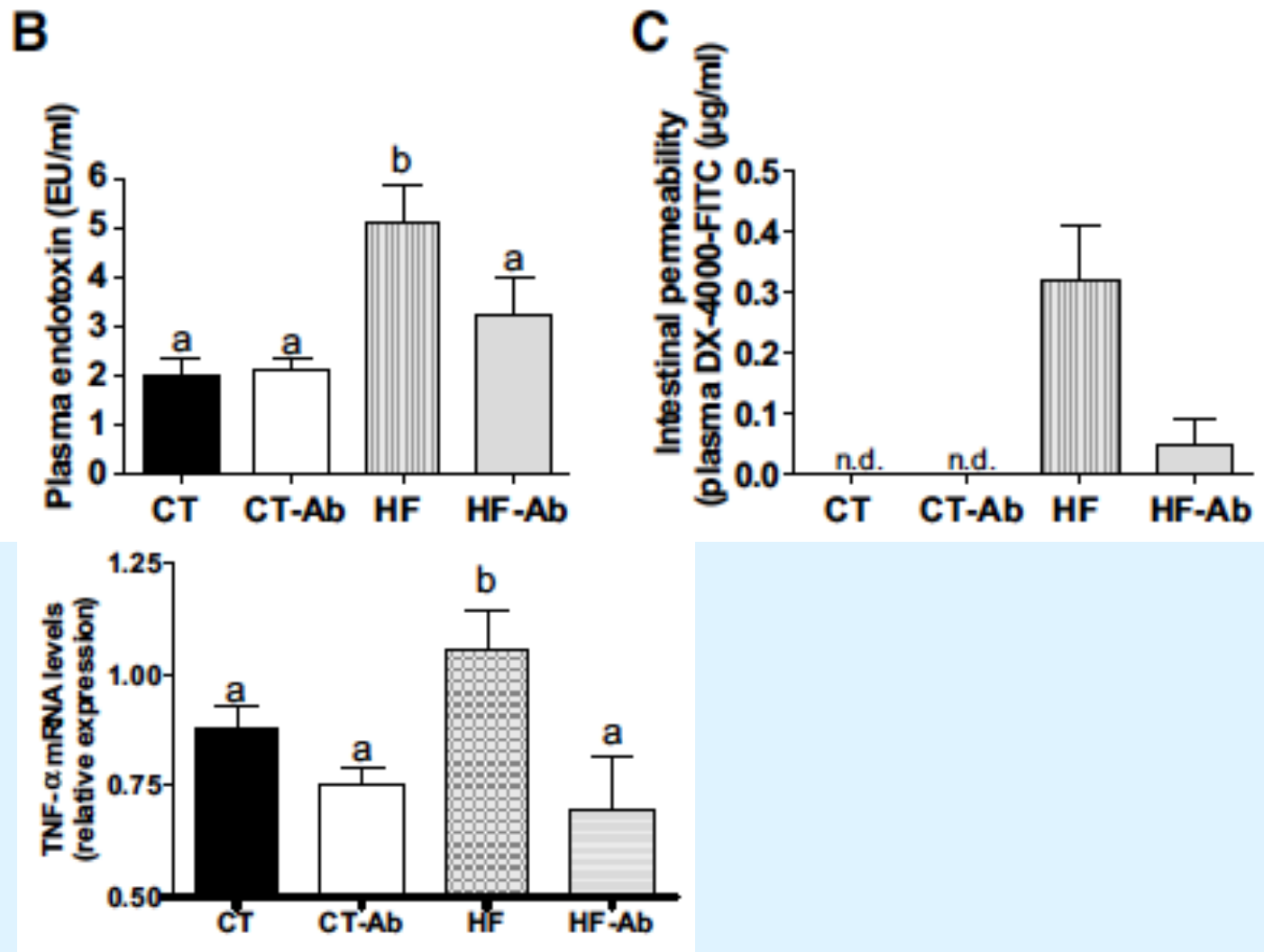


Germ-free mice resist diet-induced obesity



- Increased *Fiaf* = less fatty acid storage
- Increased AMPK/target (Acc-P) = more fatty acid oxidation

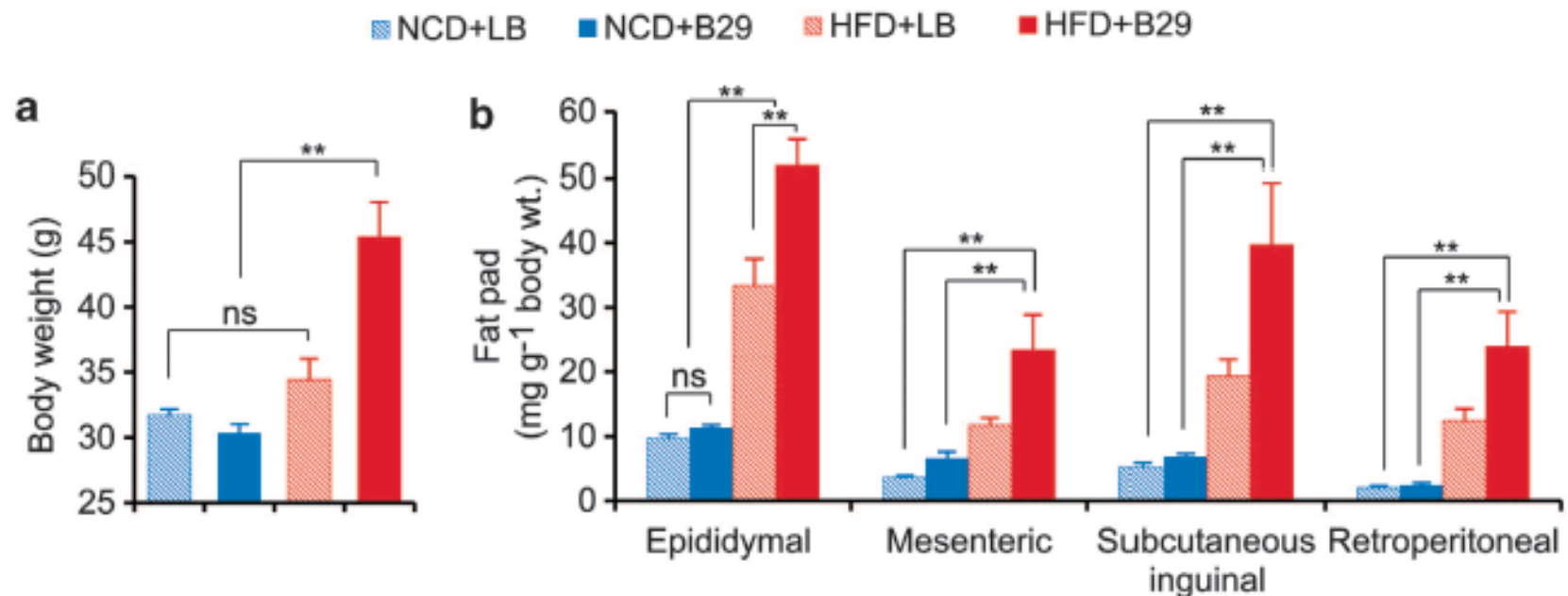
High-fat diet increases intestinal permeability



Cani et al. Diabetes 2008;57:1470-81.

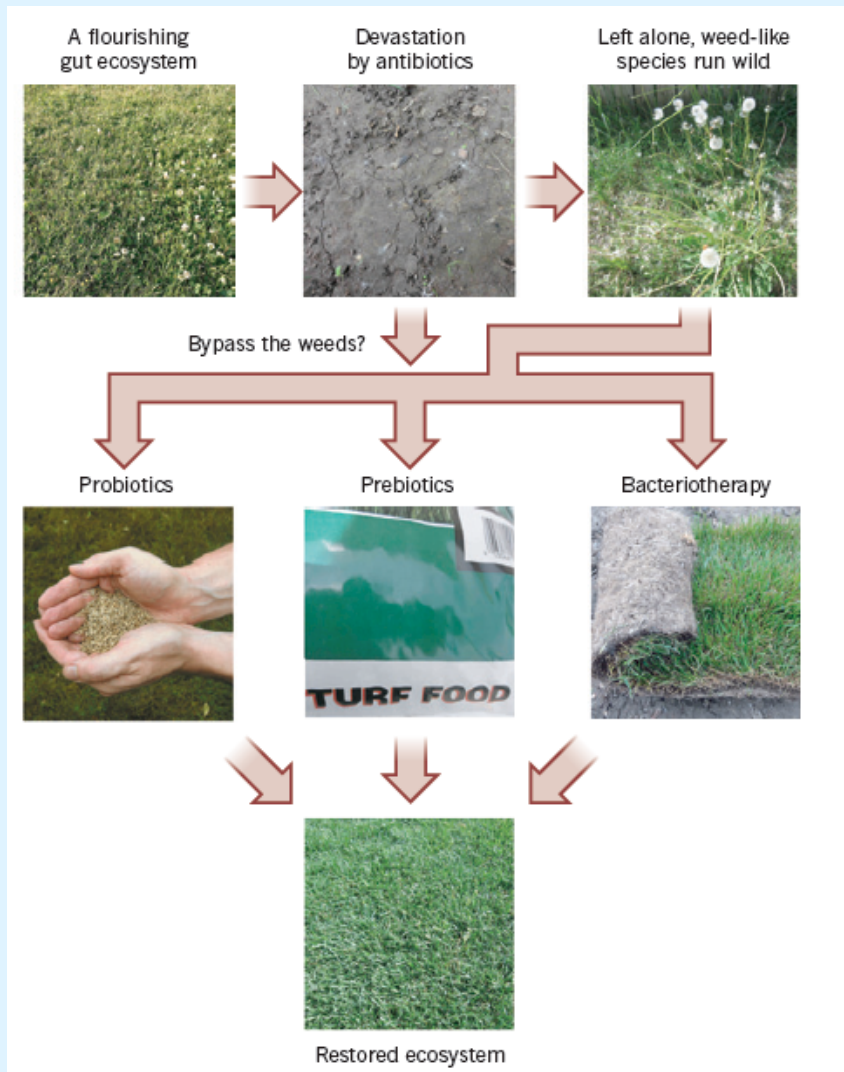
Endotoxin-producing strain from an obese patient is sufficient to promote adiposity

- Morbidly obese patient put on traditional Chinese diet
- *Enterobacter* strain B29 decreased from 35% during weight loss
- Stimulated adiposity in mice, likely due to endotoxin (LPS)



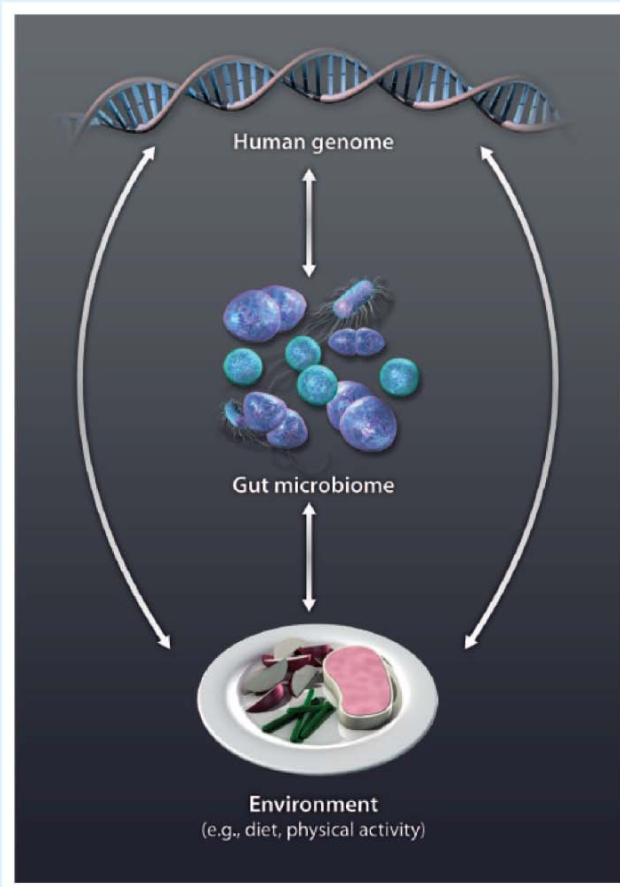
**What are the possible
clinical options?**

Options for intervention:



Alternatively: develop drugs that target key microbes or metabolic pathways

A metagenomic view of metabolism



KEY POINTS:

- Gut microbes are a key part of energy balance
- Diet, pregnancy, and low dose antibiotics alter the gut microbiome, stimulating adiposity
- Key mechanisms include fatty acid metabolism, dietary energy harvest, host-microbial signaling via SCFAs, and endotoxin production
- *Many clinical options exist, but a lot more work needs to be done*



Acknowledgements

Current lab members:



Previous lab members:

Corinne Maurice (Asst Prof; McGill)
Lawrence David (Asst Prof; Duke)
Henry Haier (Scientist; Novartis)
Alice Liou (Scientist; Pfizer)
David Gootenberg (MD/PhD; HMS)
Jesus-Mario Luevano Jr (MD; HMS)
Amy Tsou (Fellowship; Children's Hospital)
MANY wonderful summer interns!

