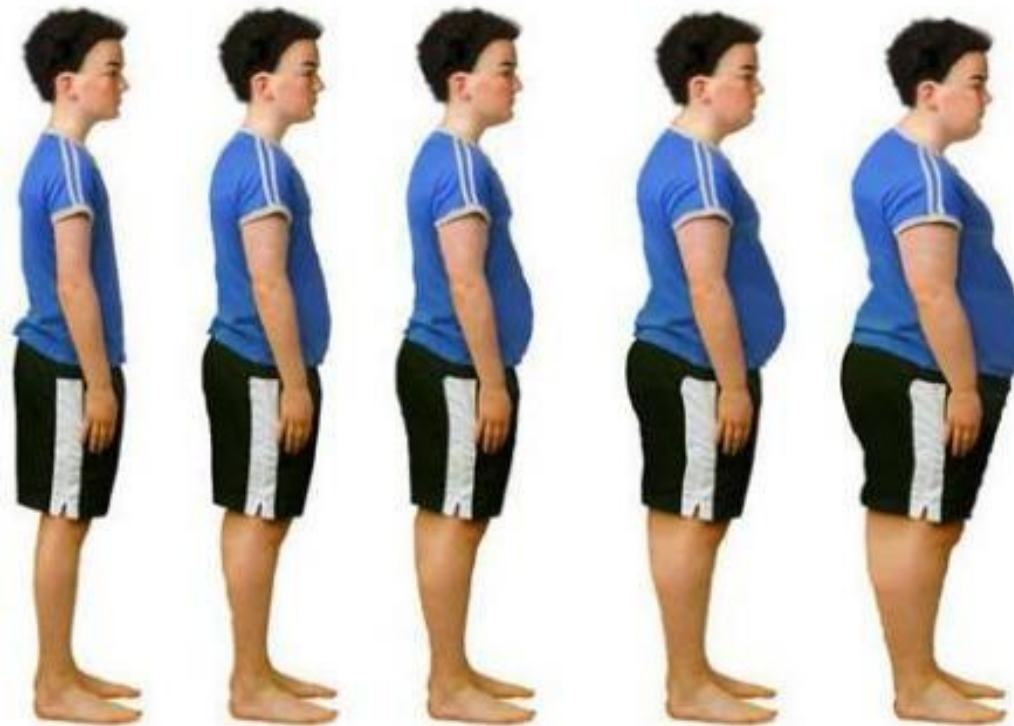


# Underlying mechanisms & causal links: high fat feeding & circadian rhythms

Fondation Merieux Conference, April 6-8, 2016

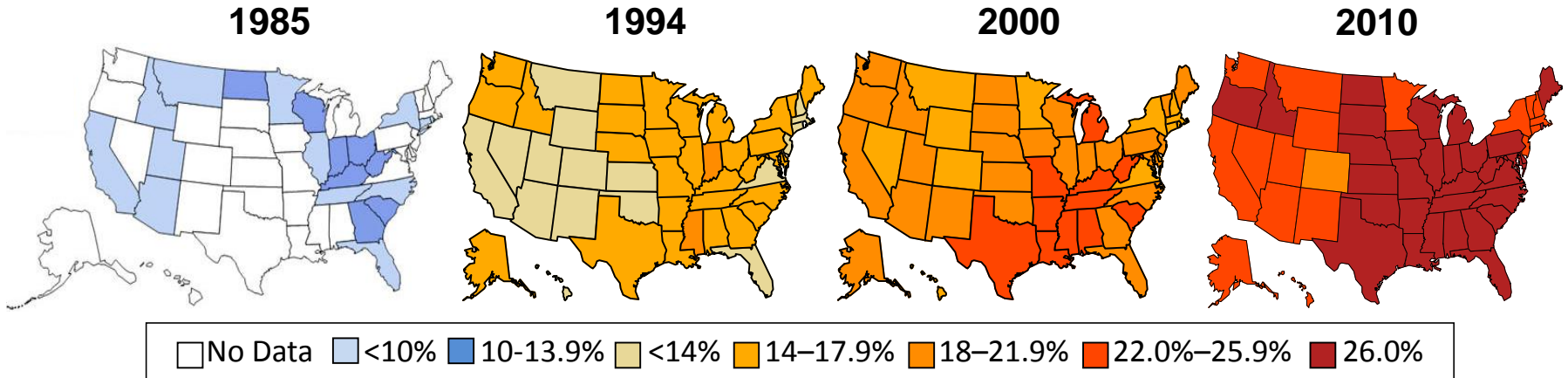
Better Foods for Better Health Microbiota & Health:  
The Challenges of a Promising Approach



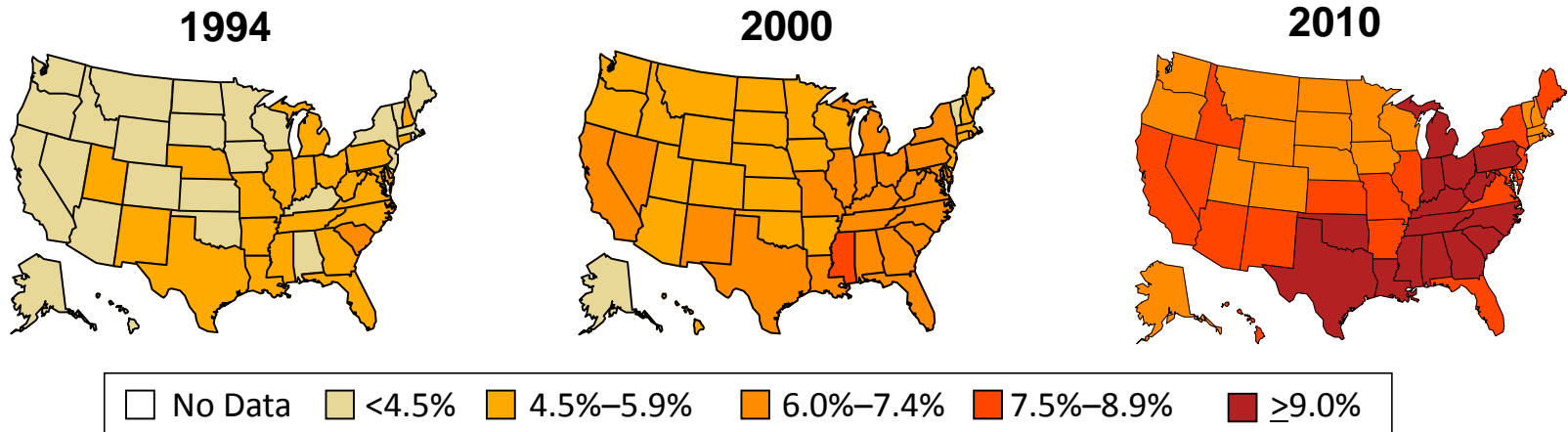
Eugene B. Chang, M.D.  
Knapp Center for Biomedical Discovery  
University of Chicago

# The obesity and diabetes epidemic

## Obesity (BMI $\geq 30\text{kg/m}^2$ )

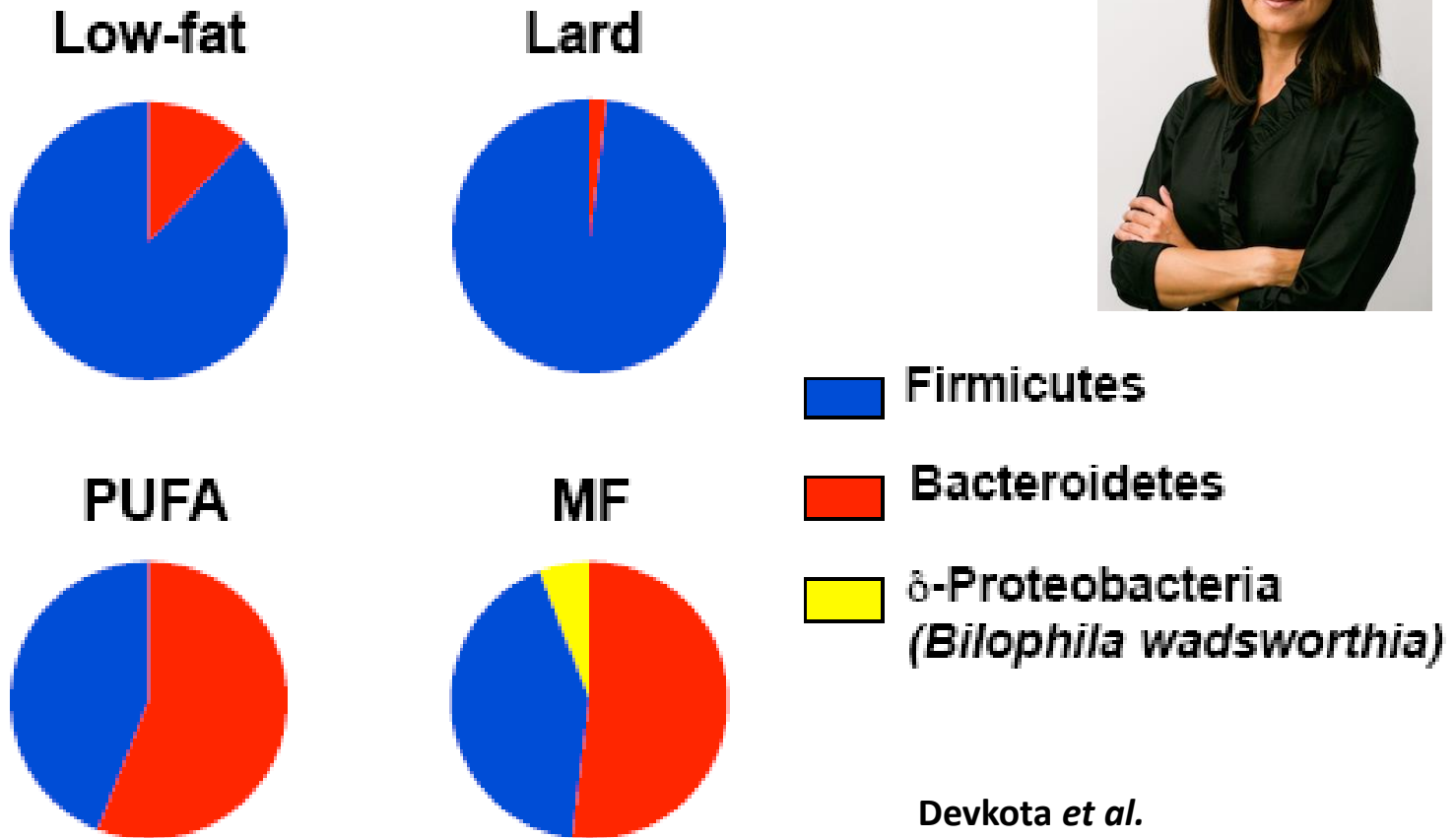


## Type 2 Diabetes



# High fat diets affect the murine enteric microbiome differently

Suzanne Devkota



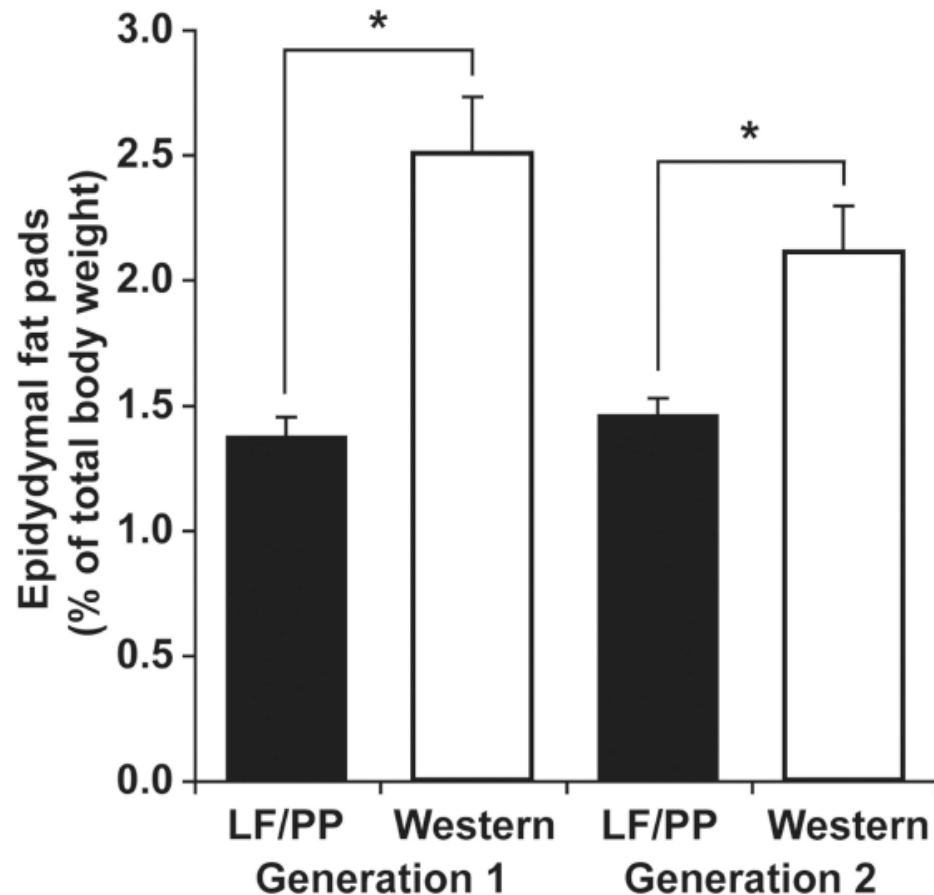
**Firmicutes**  
**Bacteroidetes**  
 **$\delta$ -Proteobacteria**  
**(*Bilophila wadsworthia*)**

Devkota *et al.*  
*Nature* (2012)

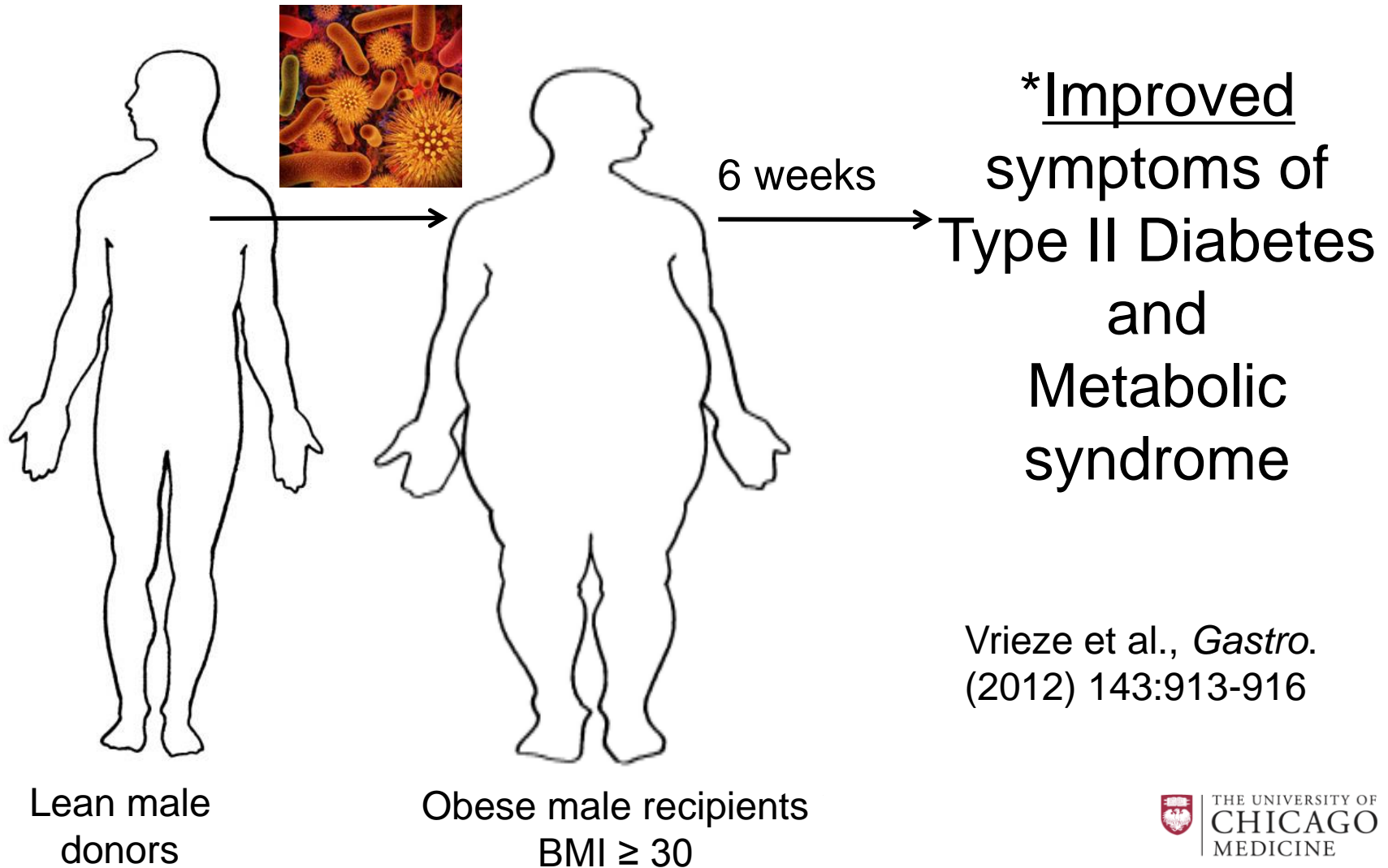
# Western-diet induced changes in humanized mouse gut microbiota promote adipose tissue

Microbiota from  
Human subjects on  
different diets  
transferred to GF mice

LF/PP – Low fat, plant polysaccharide-rich  
Western – High fat, high simple sugar



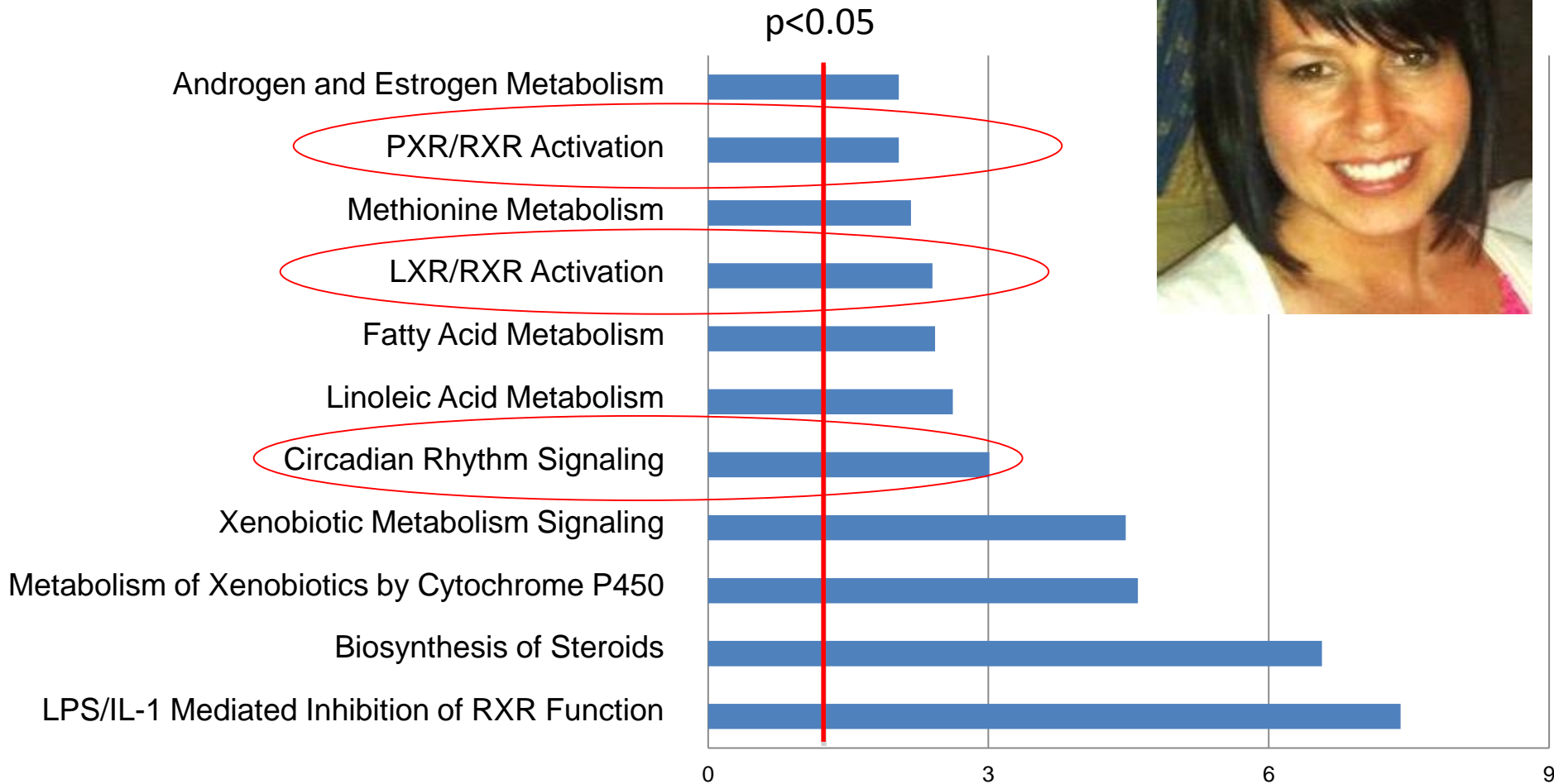
# FMT from lean donors reduces insulin resistance in obese subjects



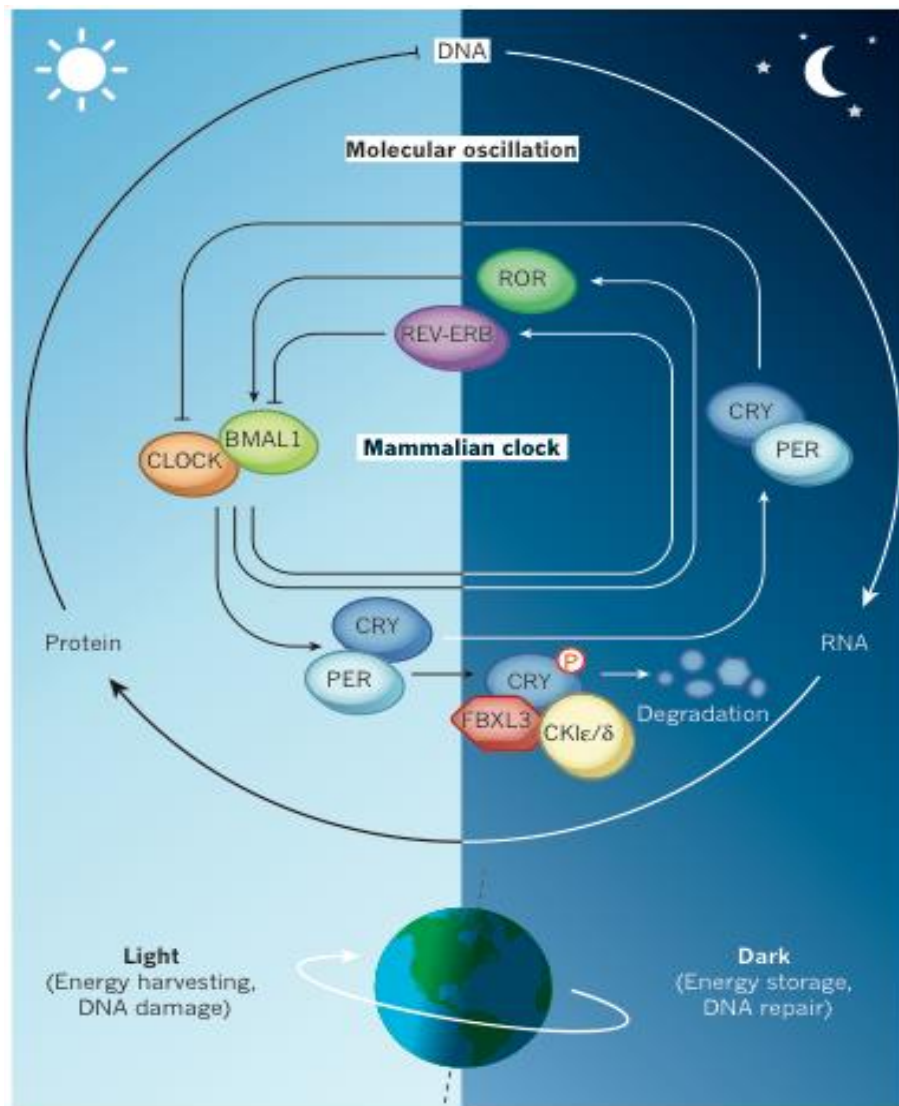
Vrieze et al., *Gastro.*  
(2012) 143:913-916

# Hepatic genes upregulated in GF versus conventionalized mice

Vanessa Leone

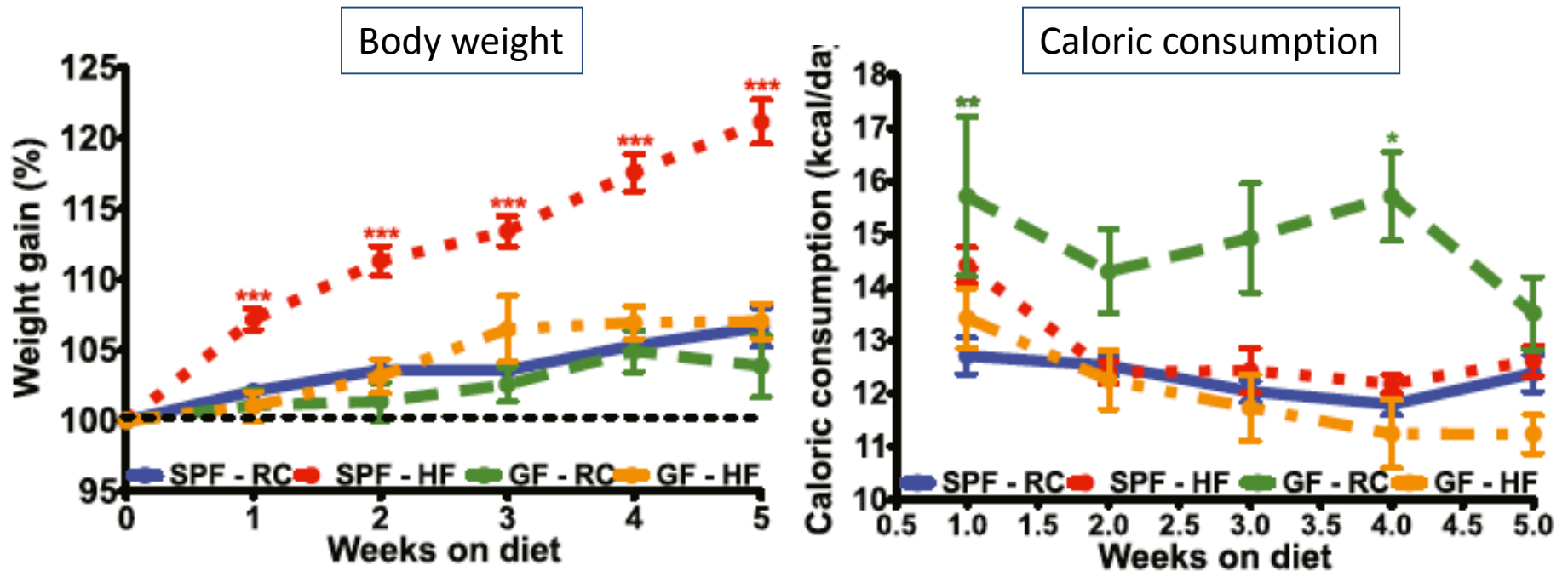


# Circadian clock networks regulate daily metabolic functions



Bass, J. Nature 2012

# Germ free (GF) mice are resistant to obesogenic diets



*n* = 17 or 18 age-matched individually housed male mice/trt group

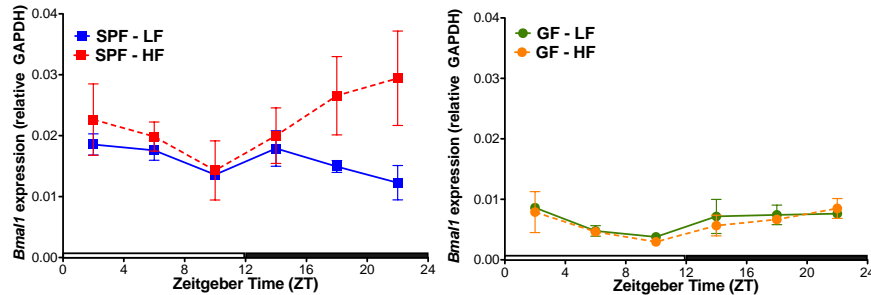


# Germ-free mice have altered circadian mediobasal hypothalamic and liver circadian clock gene expression profiles

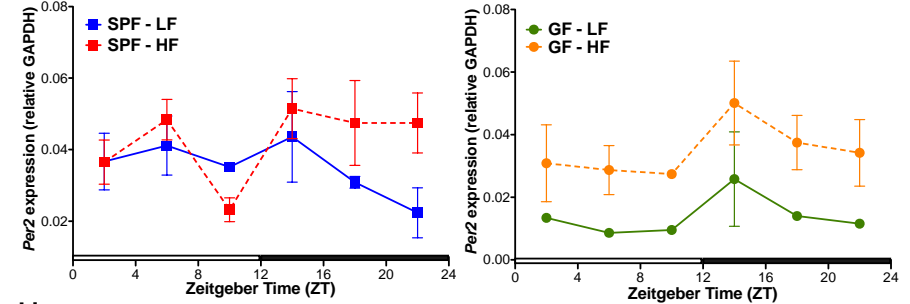
*Bmal1* (Inducer)

*Per2* (repressor)

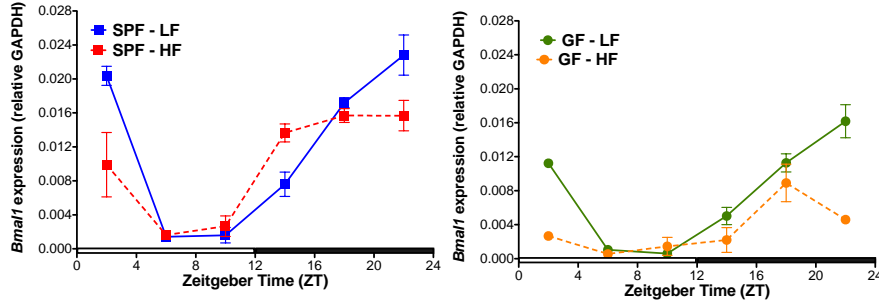
**Mediobasal hypothalamus**



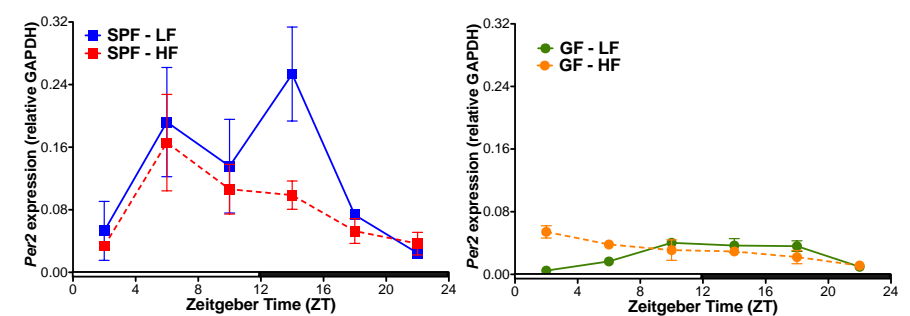
**Mediobasal hypothalamus**



**Liver**

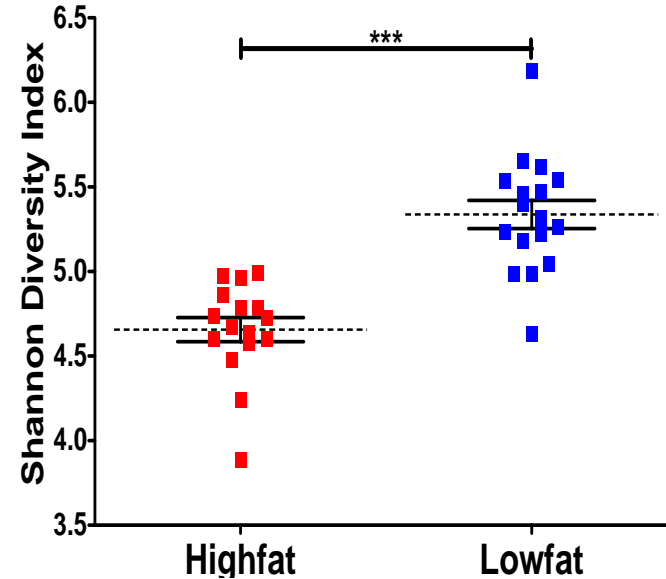
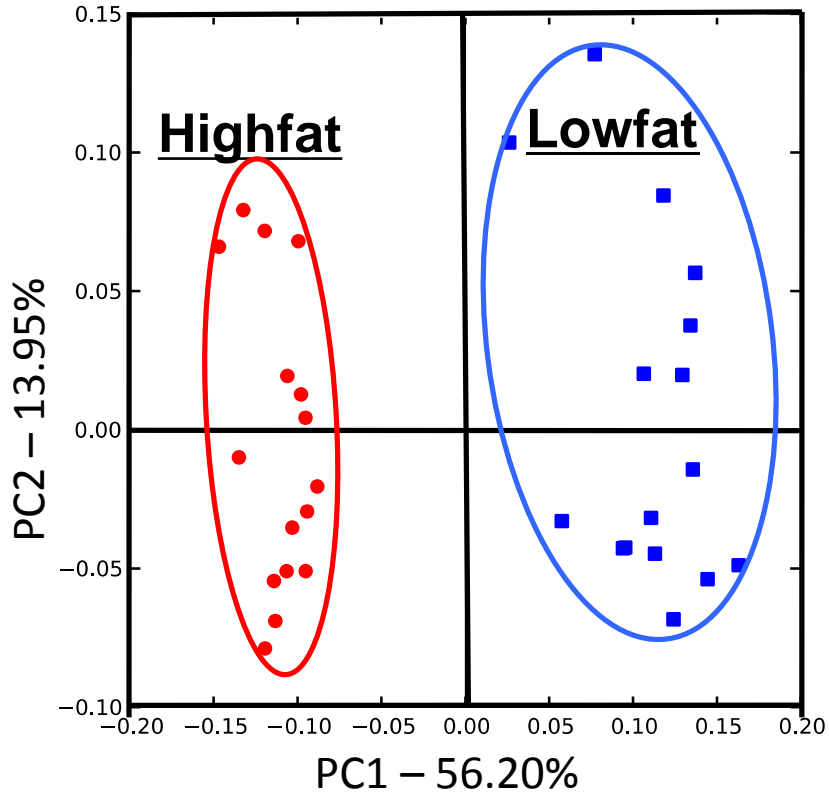


**Liver**

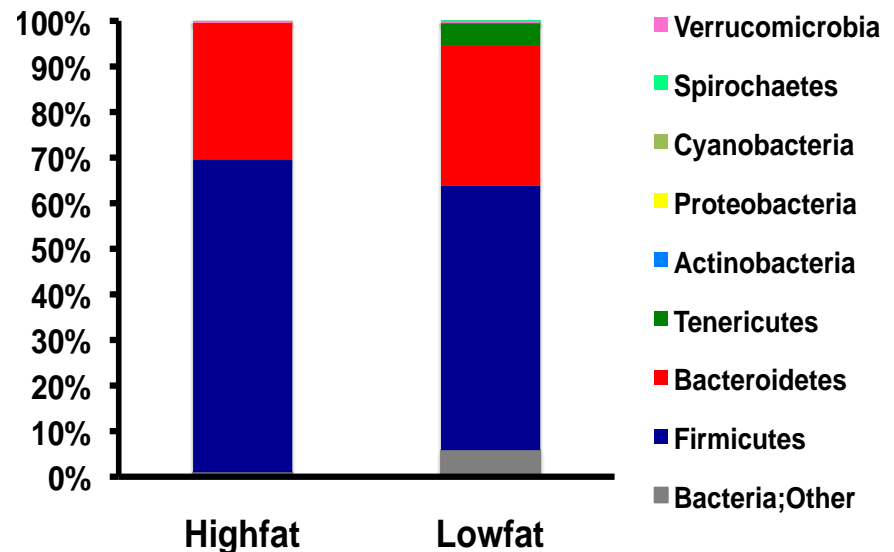


# High fat dietary intake shifts cecal microbial diversity and taxonomic structure

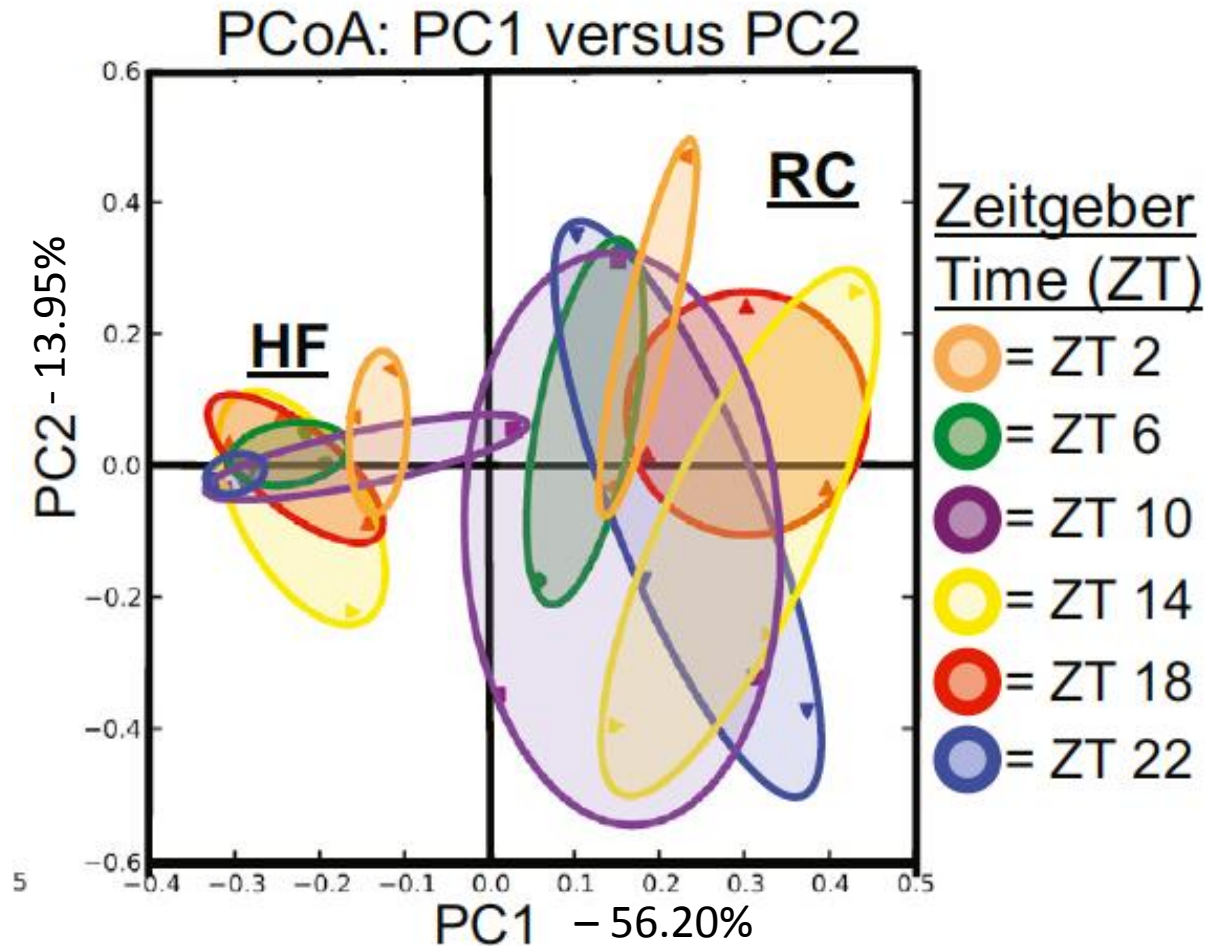
## PCoA – PC1 vs. PC2



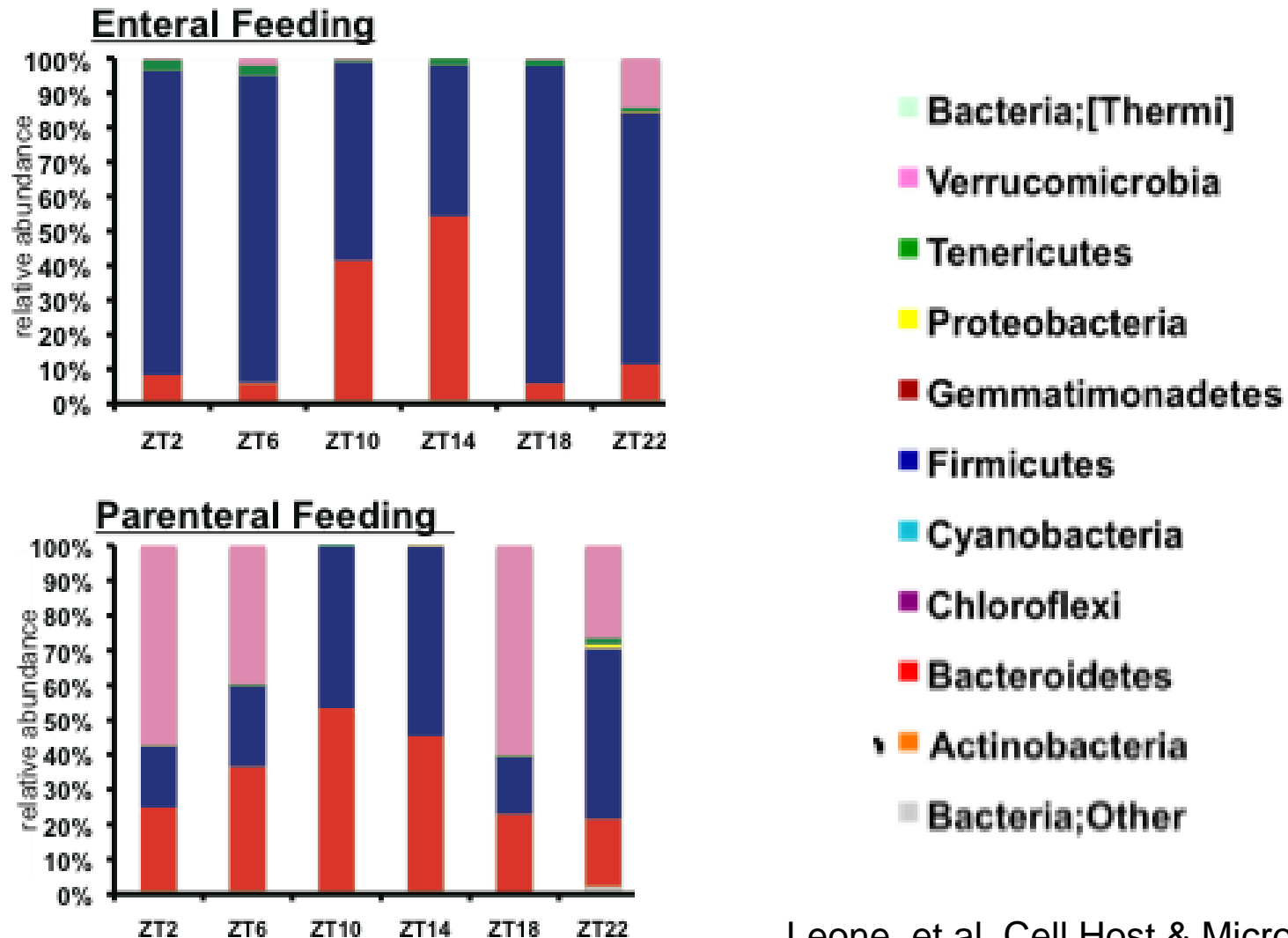
V4-V5 16s rRNA amplicon sequencing performed using Illumina Miseq



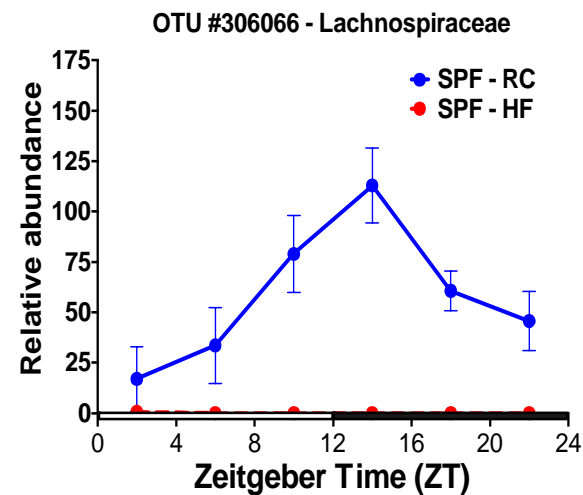
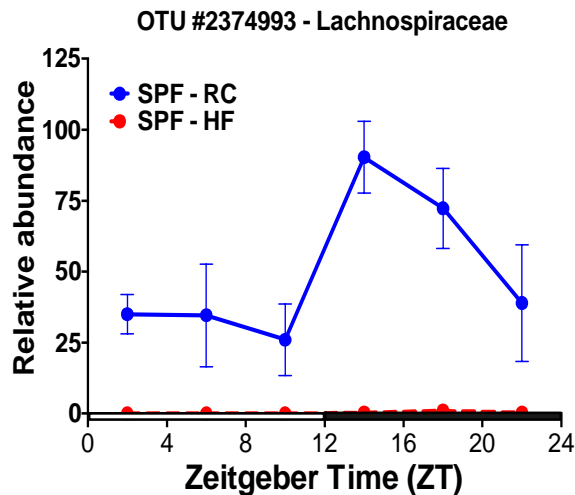
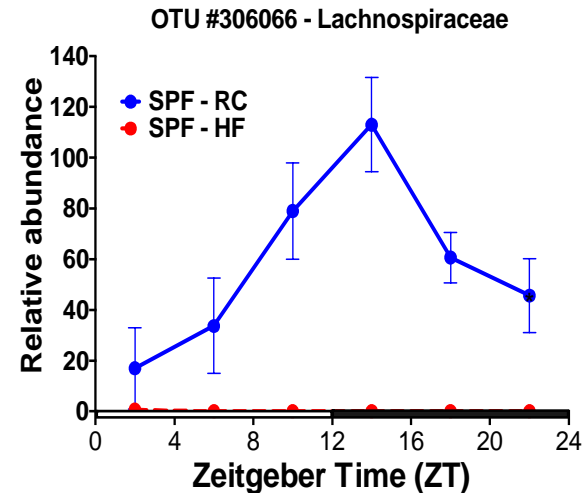
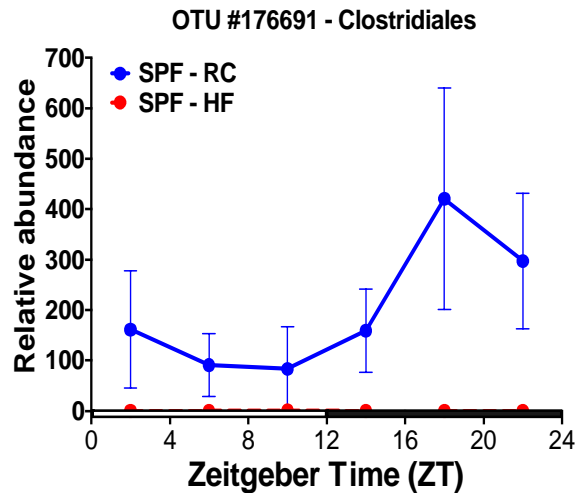
# Shifts in microbial diversity exhibit diurnal oscillations that are influenced by diet



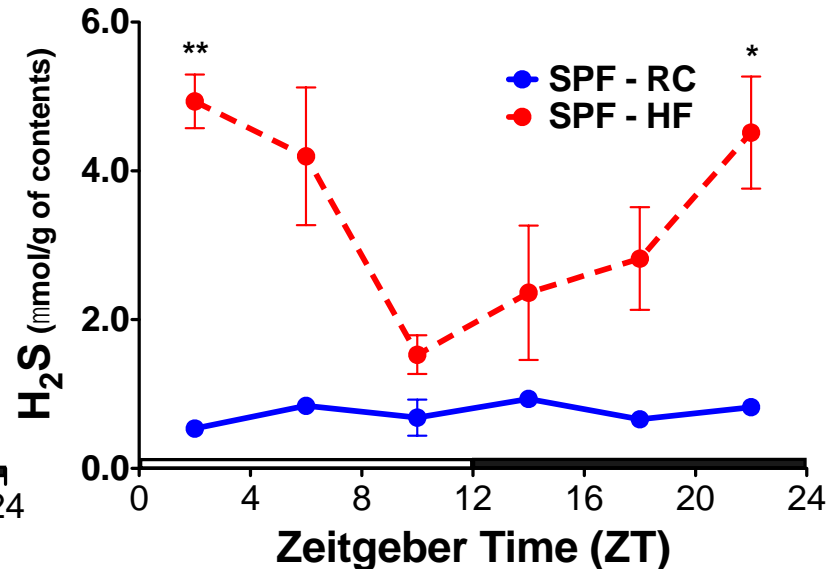
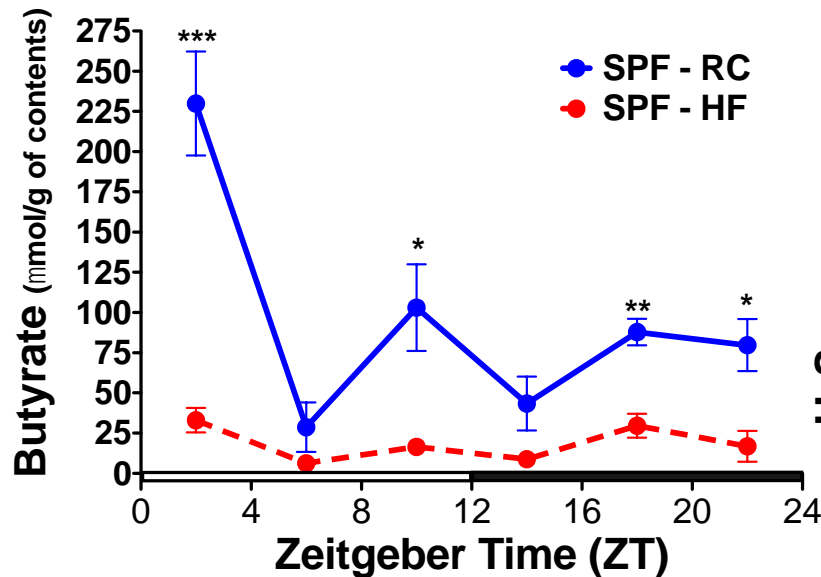
# Enteral feeding is not the only driver of diurnal variations in gut microbes



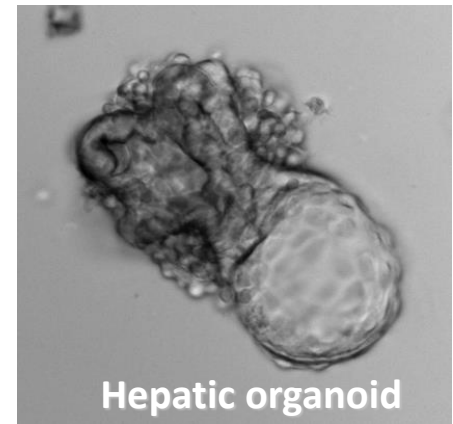
# Oscillatory cecal OTUs found in mice fed regular, low fat chow (RC) diets



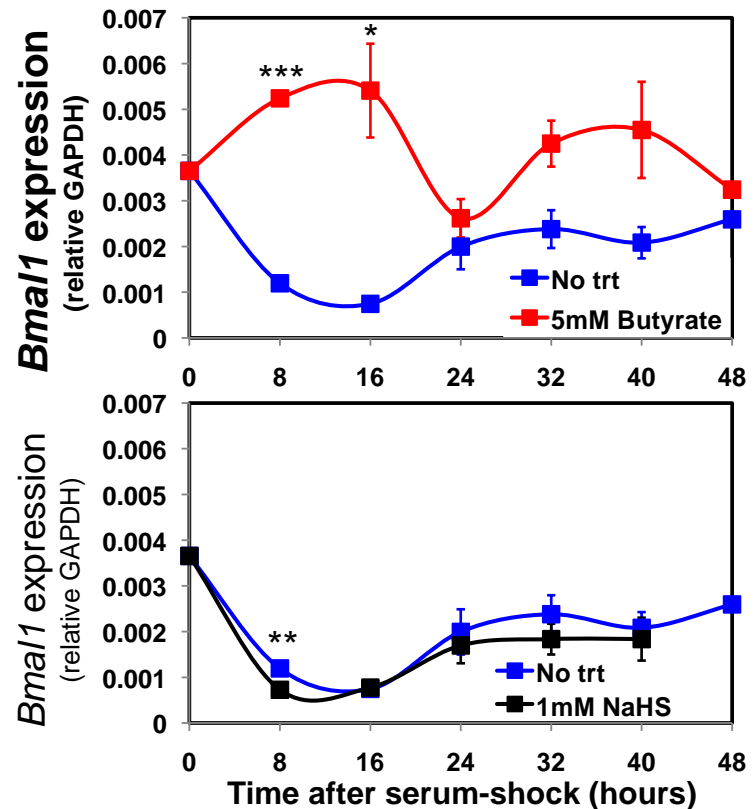
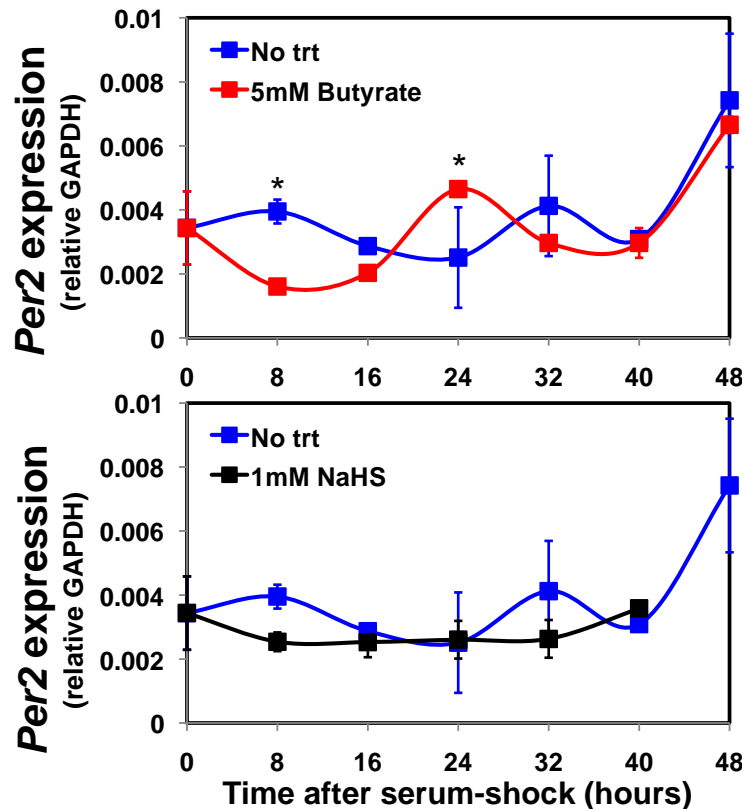
# High fat diet-induced gut microbes exhibit altered diurnal oscillations of known microbial metabolites



# Effects of SCFAs and H<sub>2</sub>S (NaHS) on hepatocyte circadian clock function

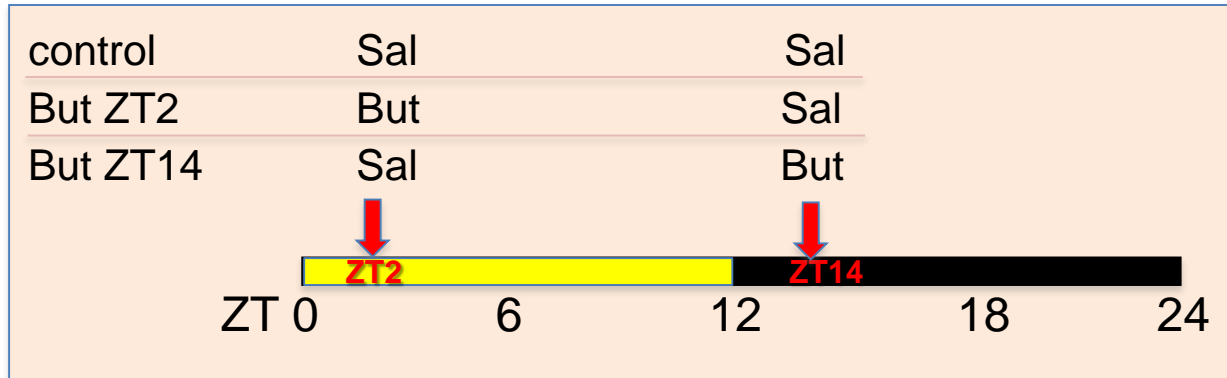


Butyrate

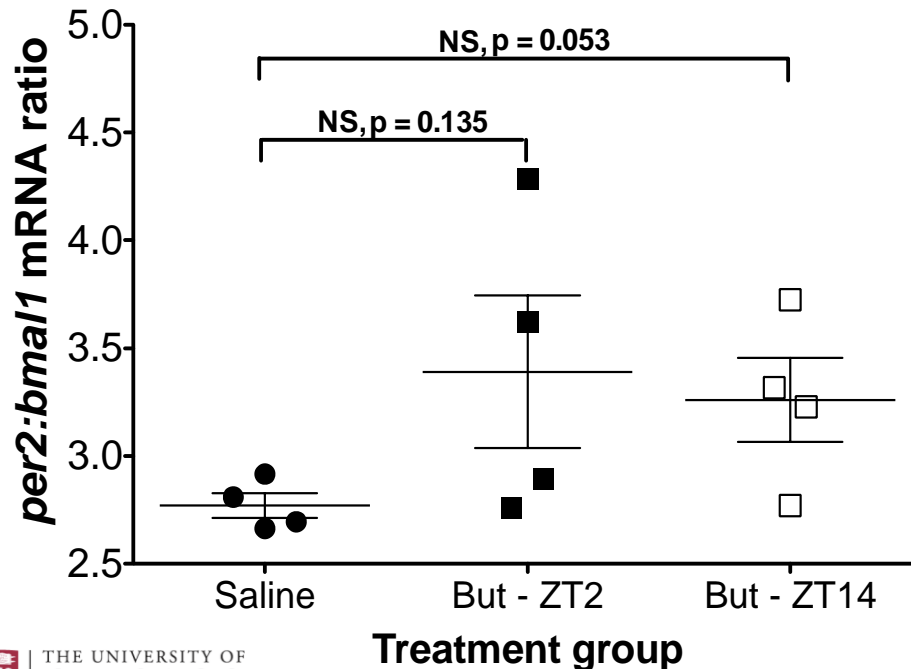


NaHS

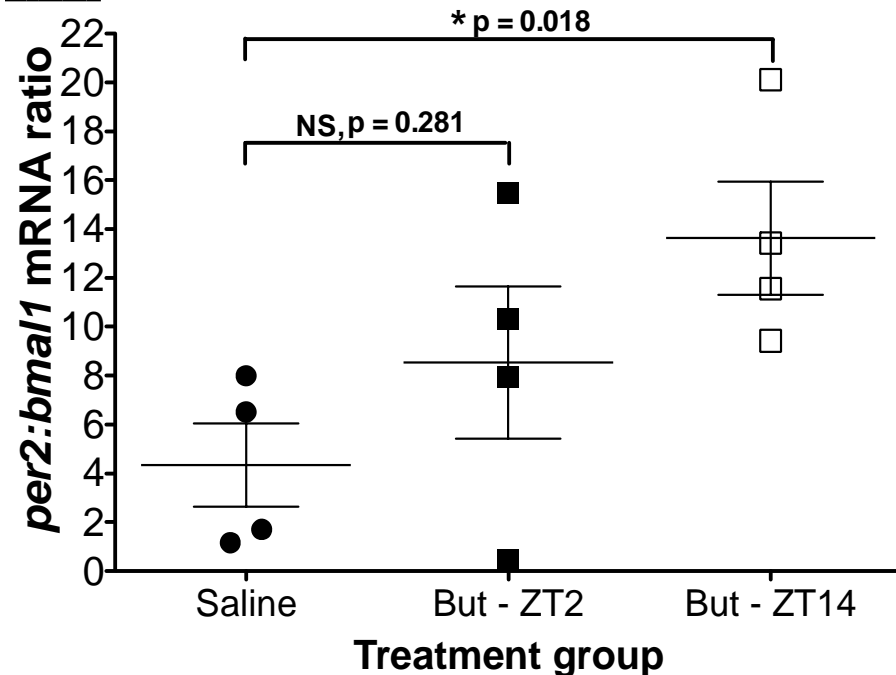
# Effects of intraperitoneal administration of butyrate on CC networks of GF mice



## Mediobasal hypothalamus



## Liver





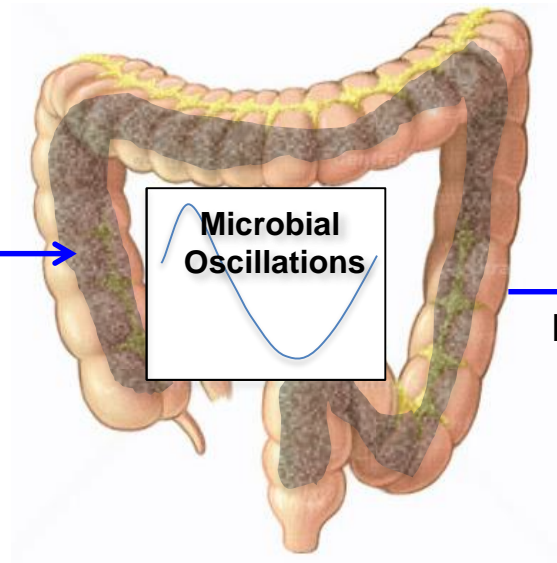
# Gut microbiota sense dietary cues and translating into an output that needed for Circadian networks

## Dietary intake

- When
- How much
- What

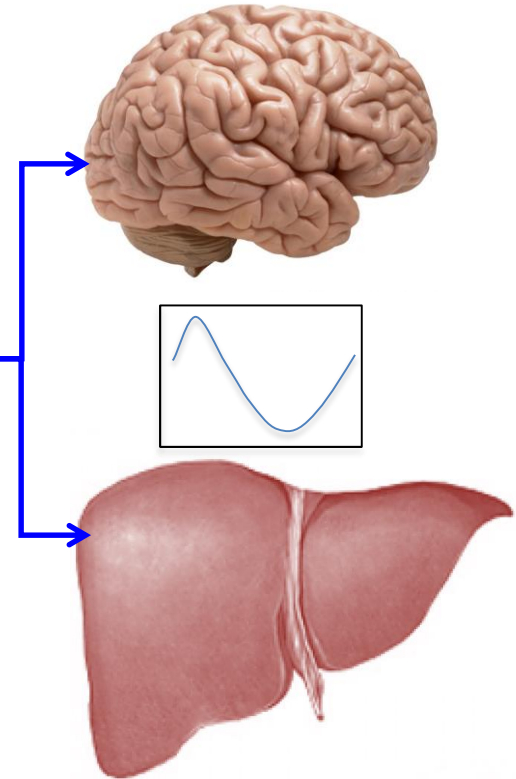


## Gut microbiota

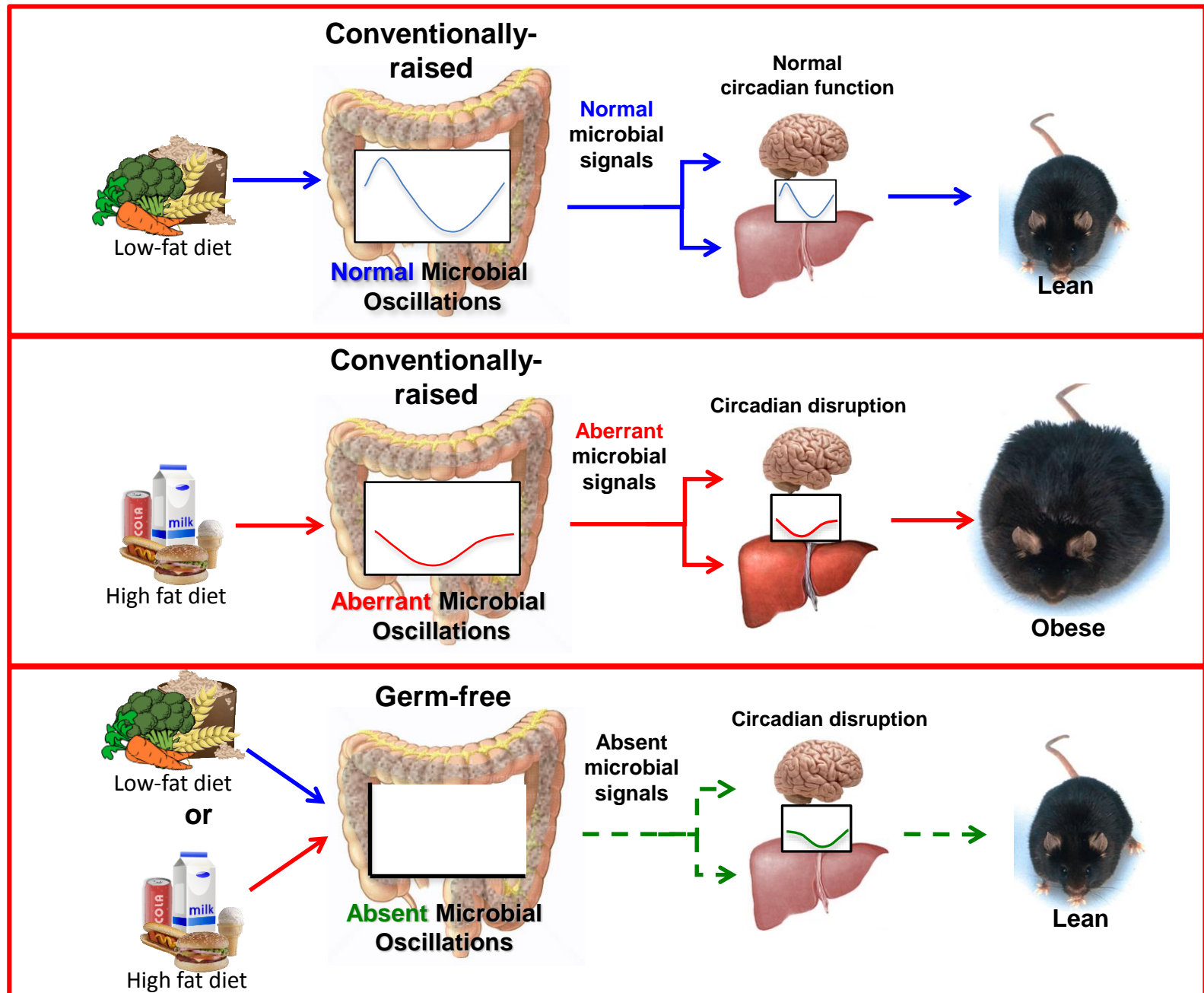


## Circadian Networks

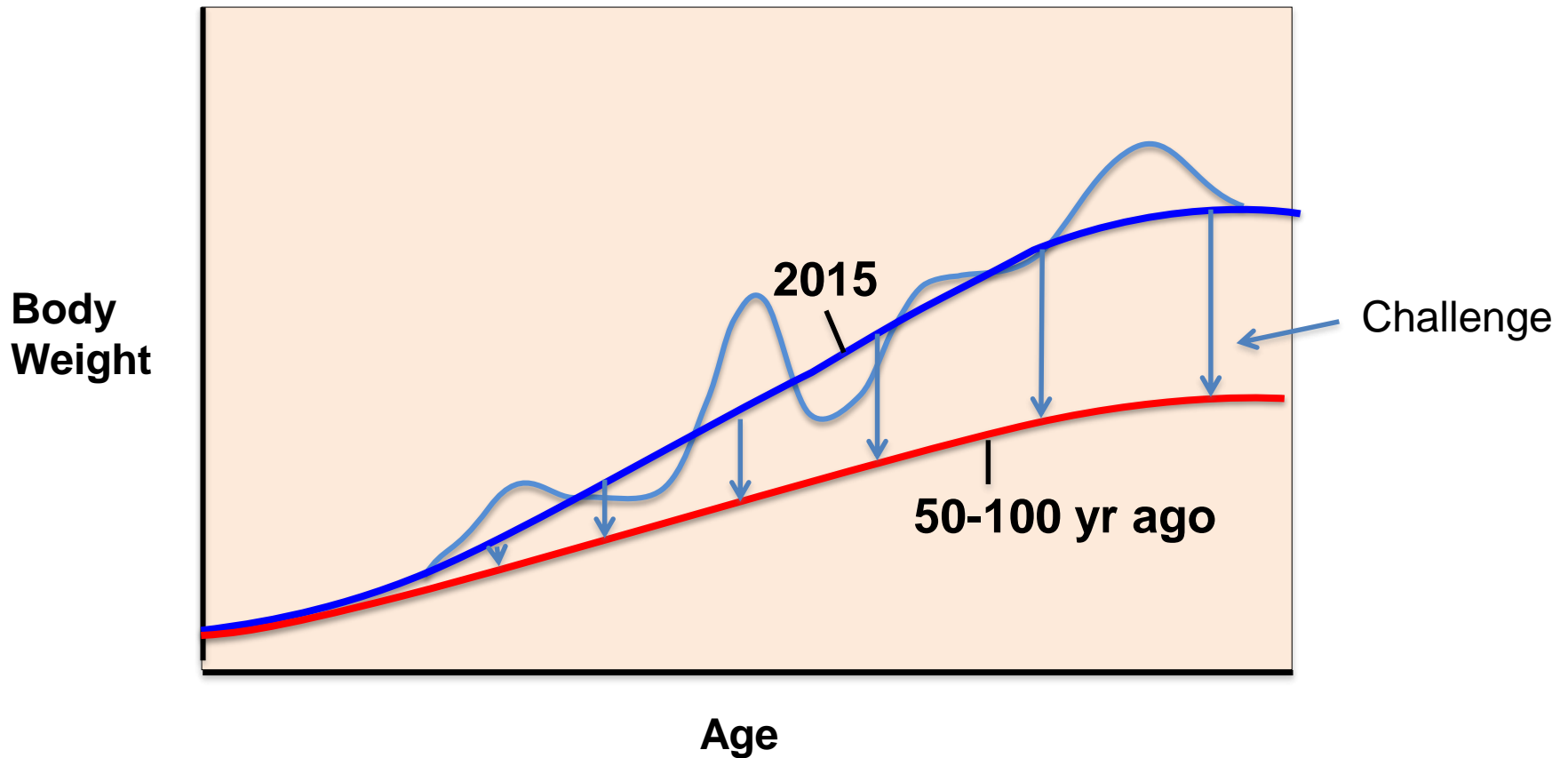
Microbial  
signals  
Metabolome



# Impact of gut microbes on host metabolism



# The challenge to treating obesity – changing energy balance



# Acknowledgements

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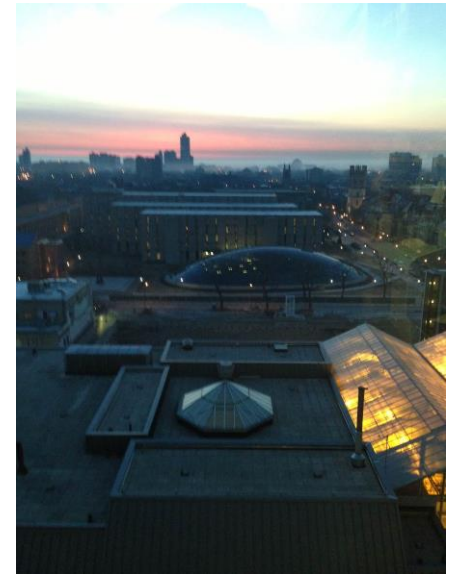
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## NutriScience

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Pam Coleman



Sunrise from the Knapp Center for Biomedical Discovery after a long circadian study

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