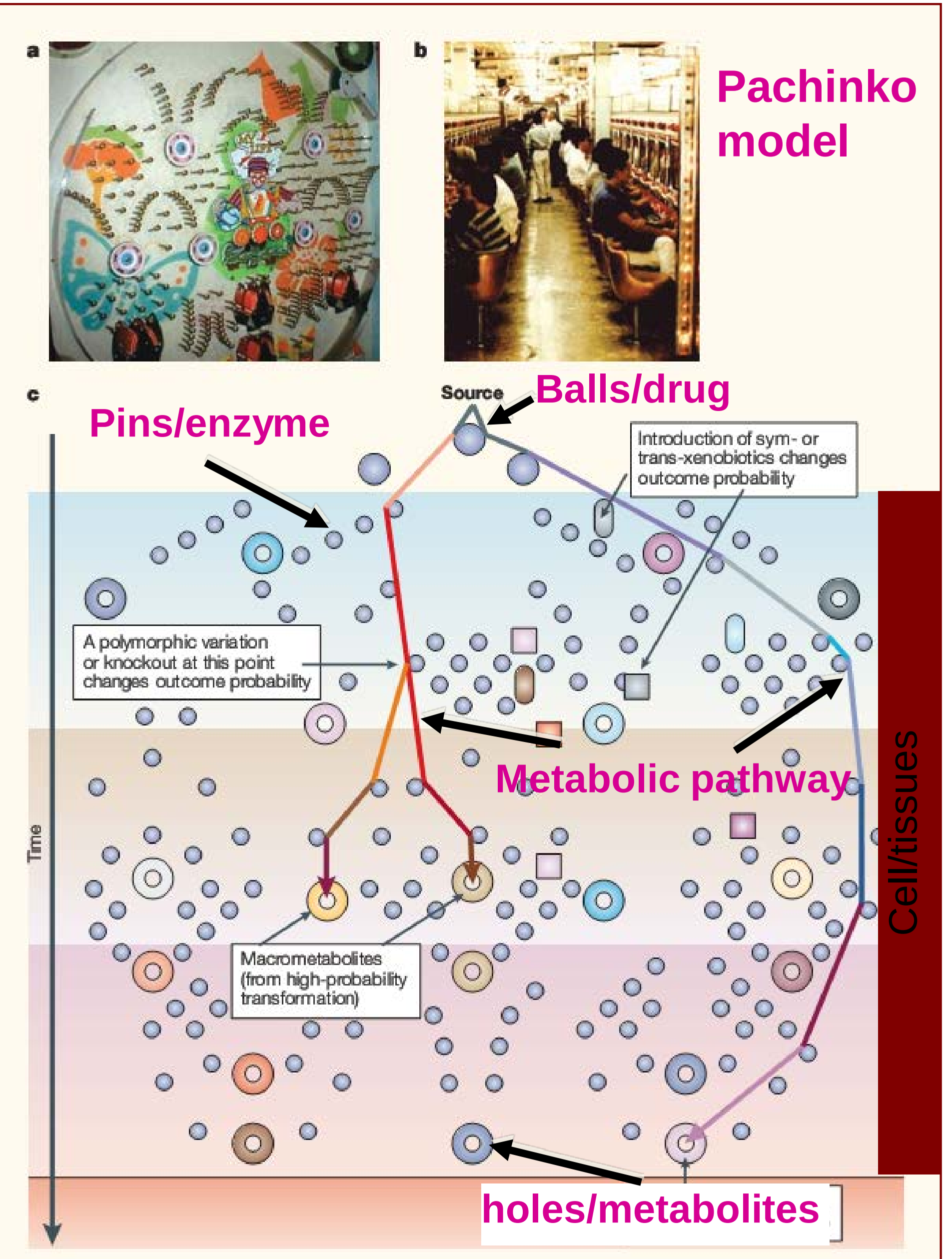
ASCPT2017-March 15-18, 2017

# Gut microbes shape mammalians' metabolism

Yulan Wang

Biomedical Metabonomics
Wuhan Institute of Physics and Mathematics
Chinese Academy of Sciences, China

# Complexity of the fate of drug




**Genetic and environmental factors**

↓

**Activity of enzyme/how the pins arranged**

↓

**Interactions of pins and balls**

↓

**Fate of metabolites/Metabolic pathway**

↓

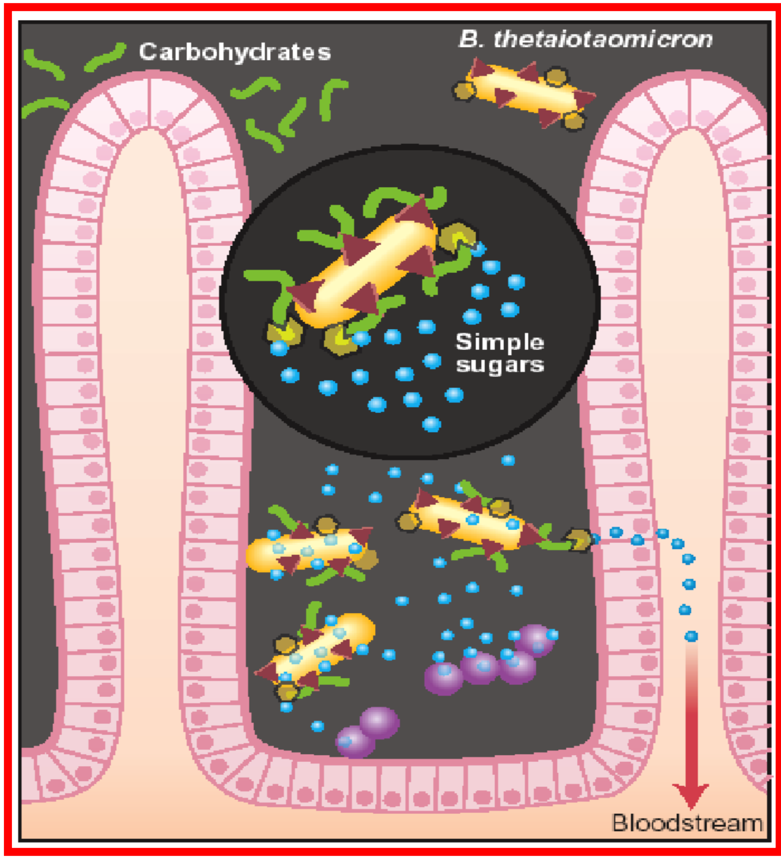
**Idiosyncratic interactions**

Nicholson, Nat Rev Drug Discovery, 2003, Vol2, 668-676

# We do not live alone

A Genomic View of the Human–*Bacteroides thetaiotaomicron* Symbiosis

Jian Xu, Magnus K. Bjursell, Jason Himrod, Su Deng, Lynn K. Carmichael, Herbert C. Chiang, Lora V. Hooper, Jeffrey I. Gordon*




**10-100 trillions of gut microbes**

1. defence against pathogens
2. development of intestinal structure
3. fermentation of dietary fibre
4. metabolite of proteins
5. play a role in drug metabolism

# Metabolomics provides method to detect the impact of gut microbes

## NMR Spectroscopy

Probe nuclei: $^{1}H$, $^{13}C$, $^{31}P$, $^{15}N$

Structure elucidation

- COSY, JRES, TOCSY
- HMQC, HMBC etc
- STOCSY family

Hyphenated techniques

- LC-SPE-MS-NMR, CE-NMR, CEC-NMR

*In situ* detection

- HR-MAS (cells + tissues)

## Mass Spectrometry

GC-MS-MS

HPLC-MS

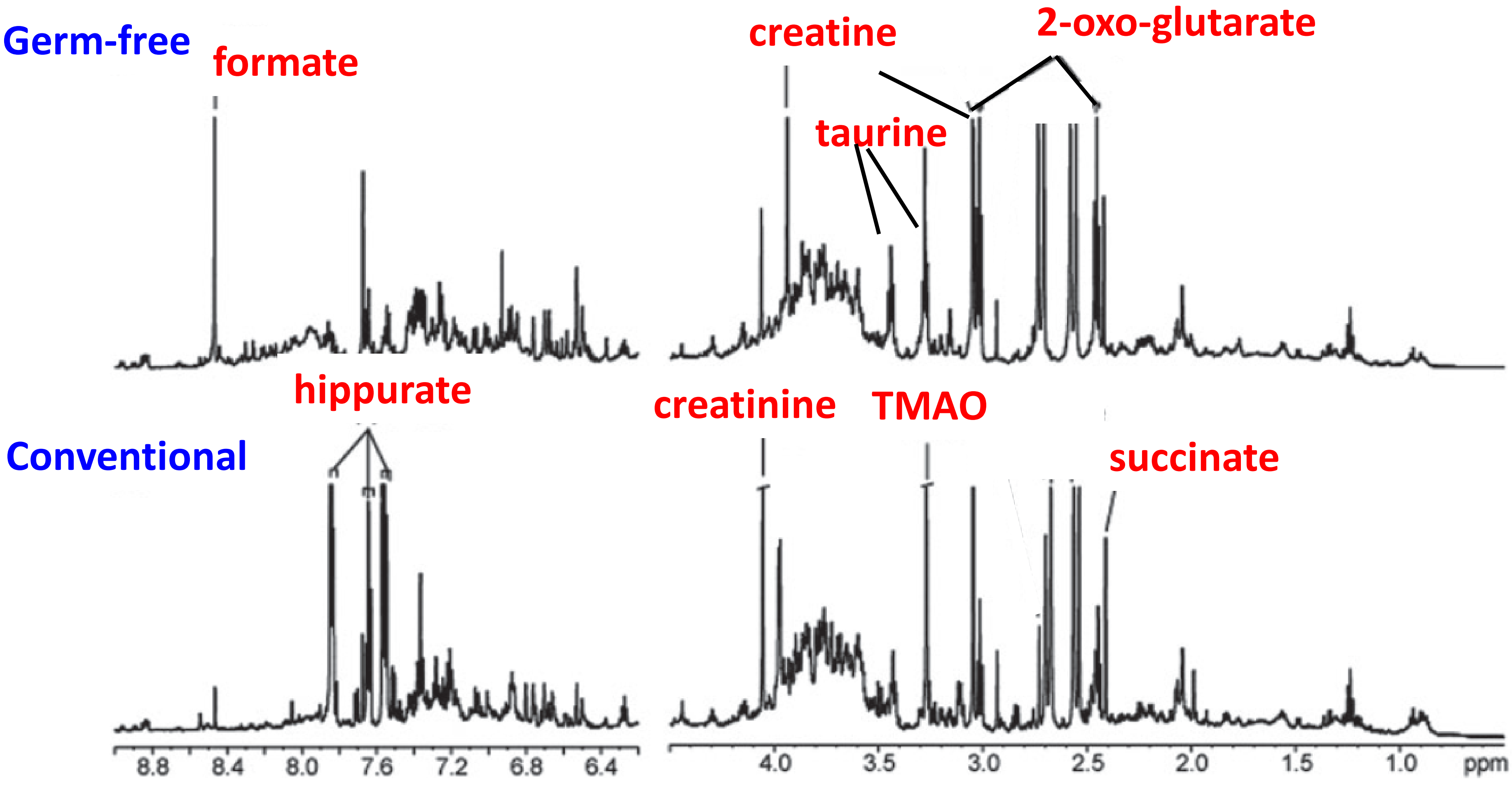
UPLC-$MS^n$

LC-ICPMS

CE-MS

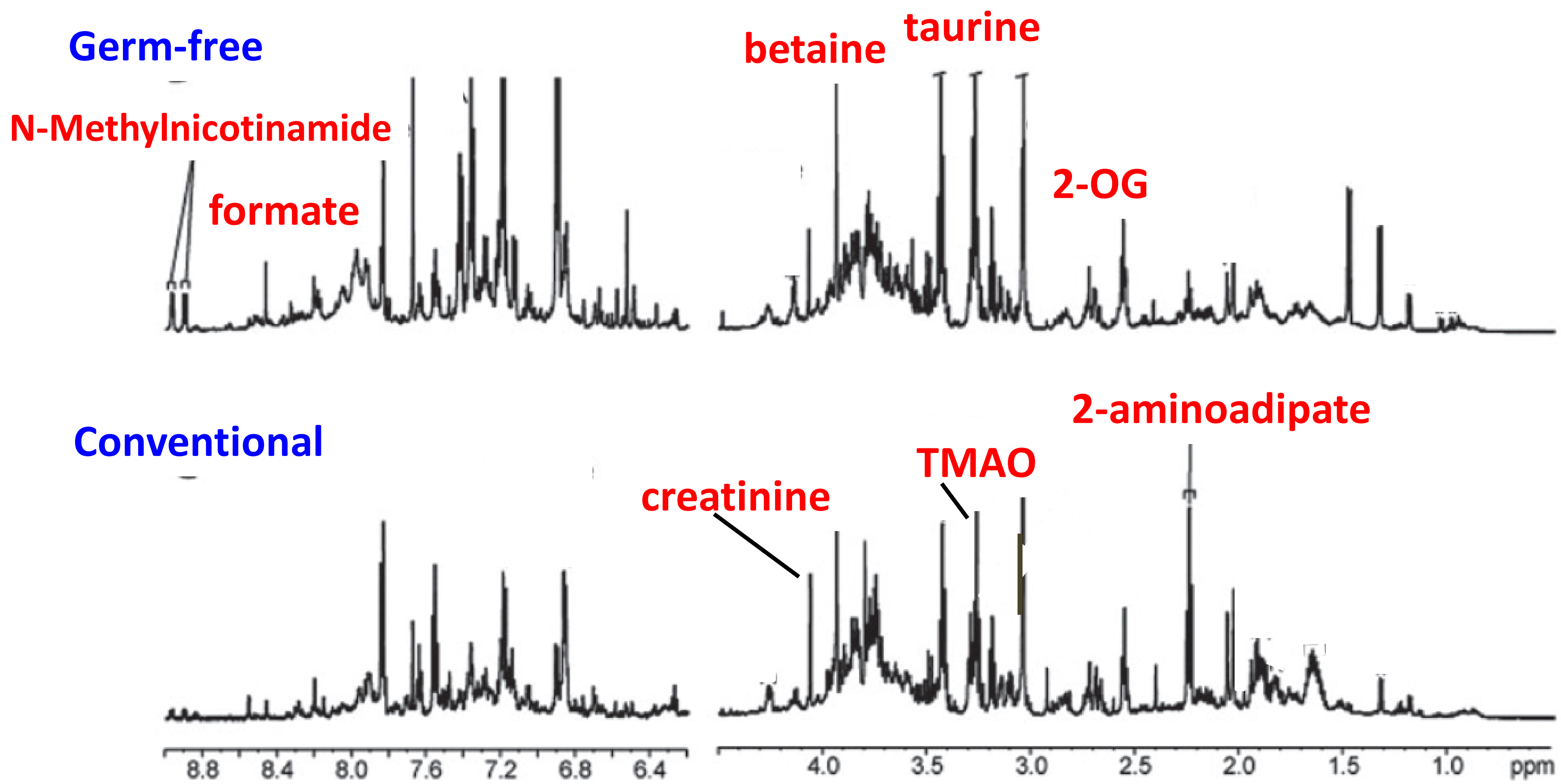
TLC/MS

# Germ-free rats showed different urinary metabolic profiles compared to conventional rats



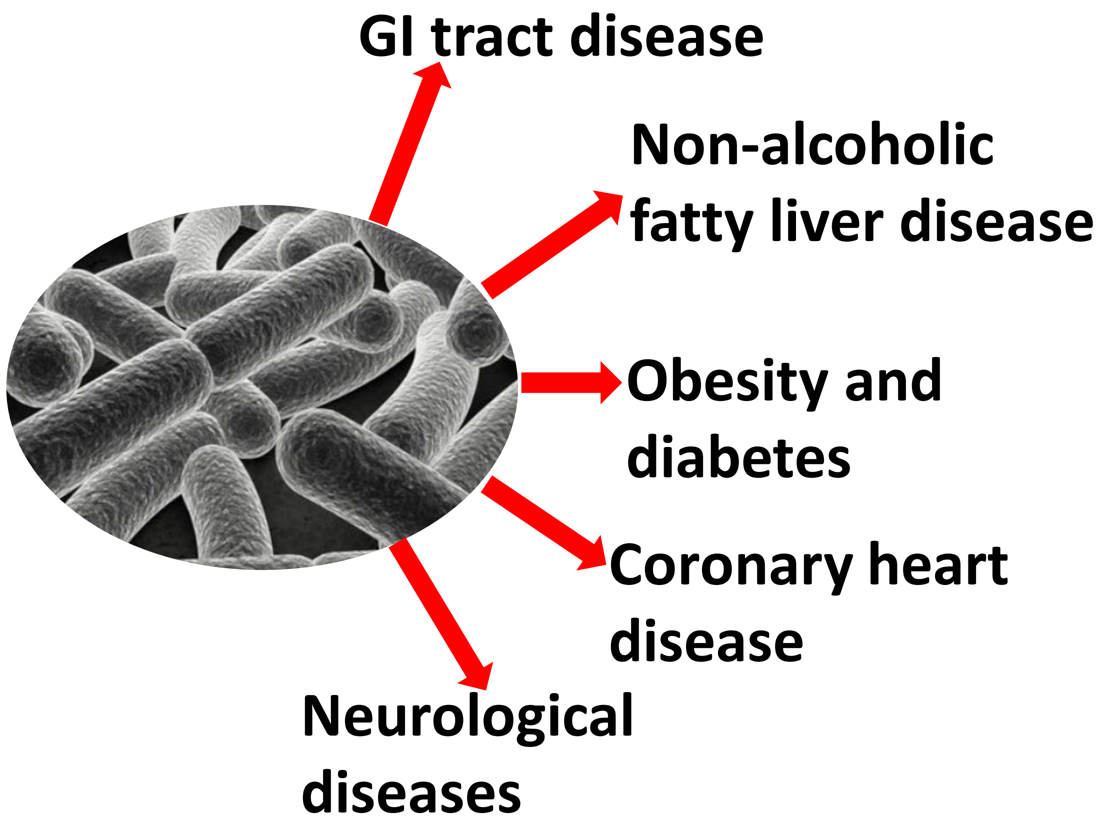

J. Swann, et al. (2009) Mol. BioSyst, 5: 351-353

# Germ-free rats showed different response to hydrazine compared to conventional rats




J. Swann, et al. (2009) Mol. BioSyst, 5: 351-353

# Diseases associated with gut microbes



# Fatty liver is associated with gut microbes

**Reconventionalized GF mice :**

- **14 days: 60%↑body fat and insulin resistance, food intakes↓**
- **Microbiota promoted absorption of monosaccharides**

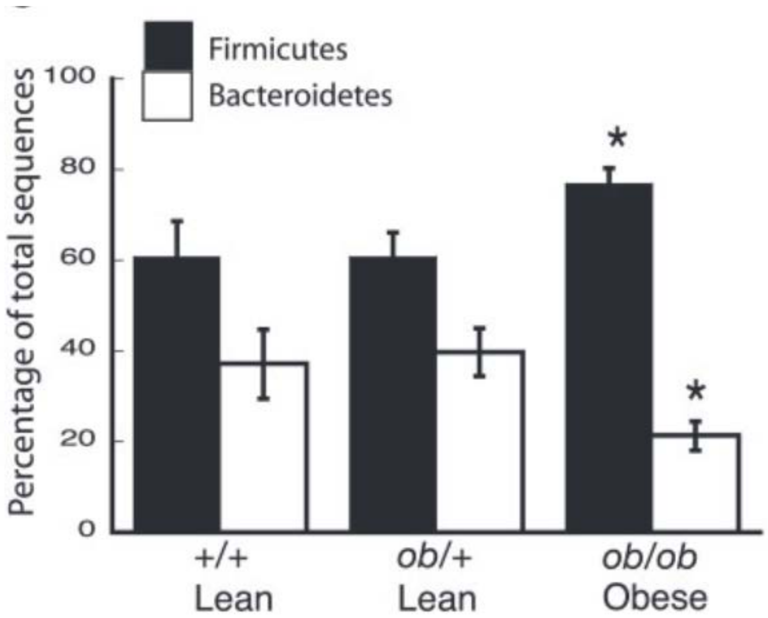
Non-digestible fibers —Microbes→ Short chain fatty acids

Short chain fatty acids → Essential for colonic cell

Short chain fatty acids → Energy source

F. Backhed, et al. (2004) PNAS, 101: 15718-15723

# Mice: Obesity is associated with gut microbes



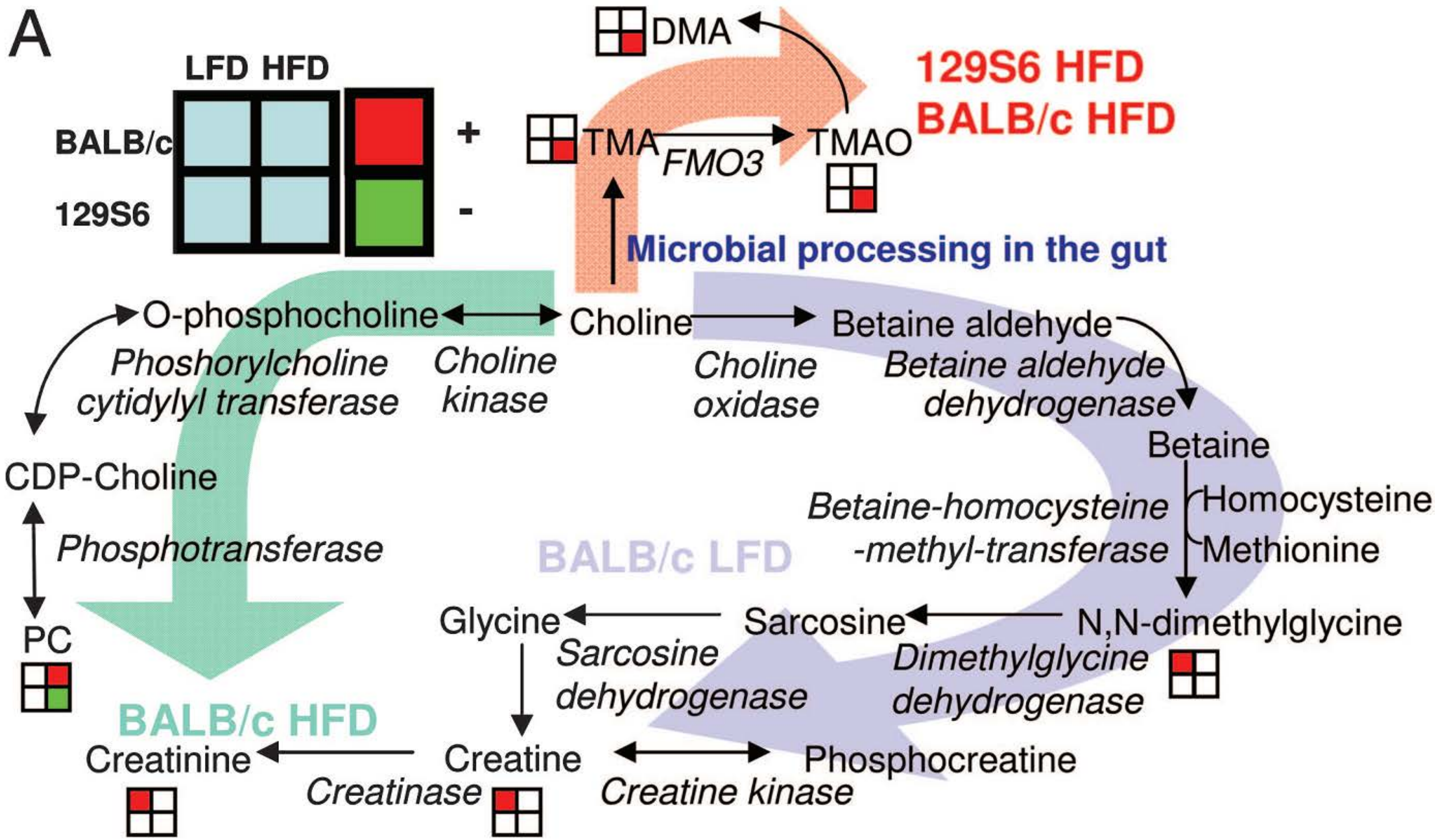

**Obese mice (ob/ob):**

- **Firmicutes/Bacteroidetes increased 50%**
- **Ob/ob mice harvest more energy from food**

R. Ley, et al. (2005) PNAS, 102: 11070-11075

# Insulin resistance and metabonomoic dysfunctions

## M. Dumas, PNAS, 2006, Vol33, 12511-12516



# Coronary Heart Disease is associated with microbes

*Nature*. 2011 April 7; 472(7341): 57–63. doi:10.1038/nature09922.

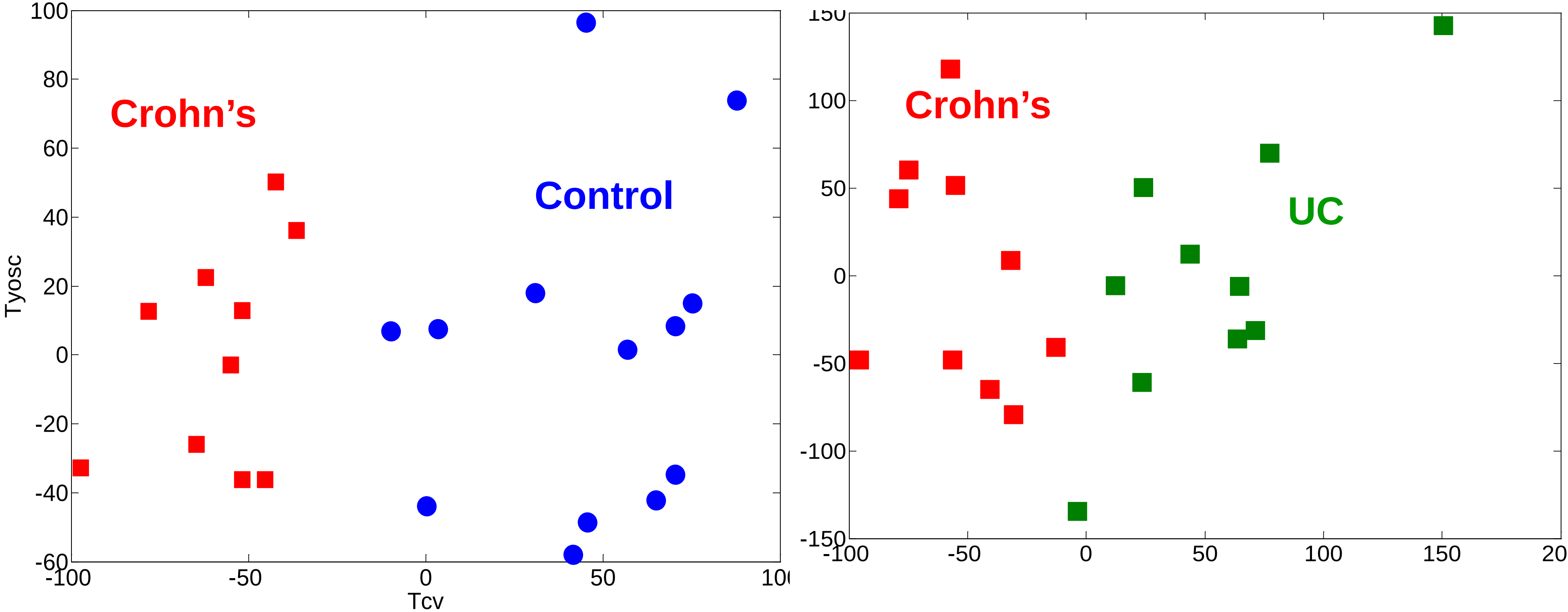
## Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

**Zeneng Wang**[1,2], **Elizabeth Klipfell**[1,2], **Brian J. Bennett**[3], **Robert Koeth**[1], **Bruce S. Levison**[1,2], **Brandon DuGar**[1], **Ariel E. Feldstein**[1,2], **Earl B. Britt**[1,2], **Xiaoming Fu**[1,2], **Yoon-Mi Chung**[1,2], **Yuping Wu**[4], **Phil Schauer**[5], **Jonathan D. Smith**[1,6], **Hooman Allayee**[7], **W. H. Wilson Tang**[1,2,6], **Joseph A. DiDonato**[1,2], **Aldons J. Lusis**[3], and **Stanley L. Hazen**[1,2,6,8]

Phosphatidylcholine-d9 —(Microbes)→ Trimethylamine-d9 → CV

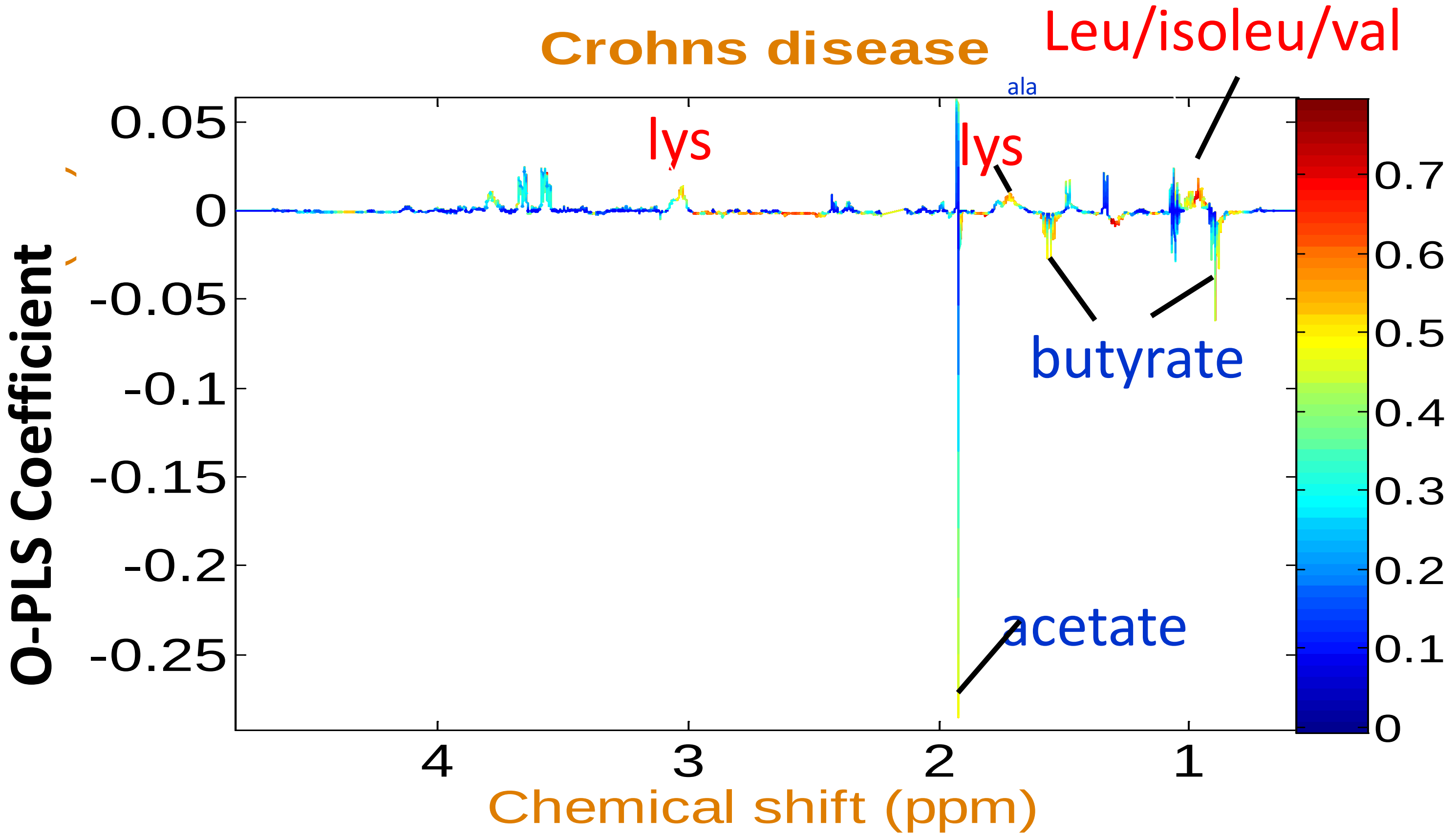
**Question: Diabetes and CV share common gut microbes**

# Metabonomics investigation showed differences in fecal extracts between control and IBD patients




Marchesi et al. J. Proteome Res., 6:546-551, 2007

# Inflammatory bowel disease are associated with reduced levels of short chain fatty acids




Marchesi et al. J. Proteome Res., 6:546-551，2007

# Neurological Disorder is associated with microbes

**Table 2 Beneficial bacteria from stool analysis**

| | Autism/ Aspergers | Control | *P*-value | % Difference |
|---|---|---|---|---|
| *Bifidobacterium* | 1.6 ± 1.9 | 2.8 ± 1.8 | 0.002 | -44% |
| *E.coli* | 2.8 ± 1.7 | 2.4 ± 1.6 | n.s. | |
| *Lactobacillus* | 2.6 ± 1.4 | 1.3 ± 1.4 | 0.00002 | +100% |
| *Enterococcus* | 0.81 ± 1.4 | 0.97 ± 1.2 | 0.05 W | -16% |

**Reduction of fatty acids is associated with autism**

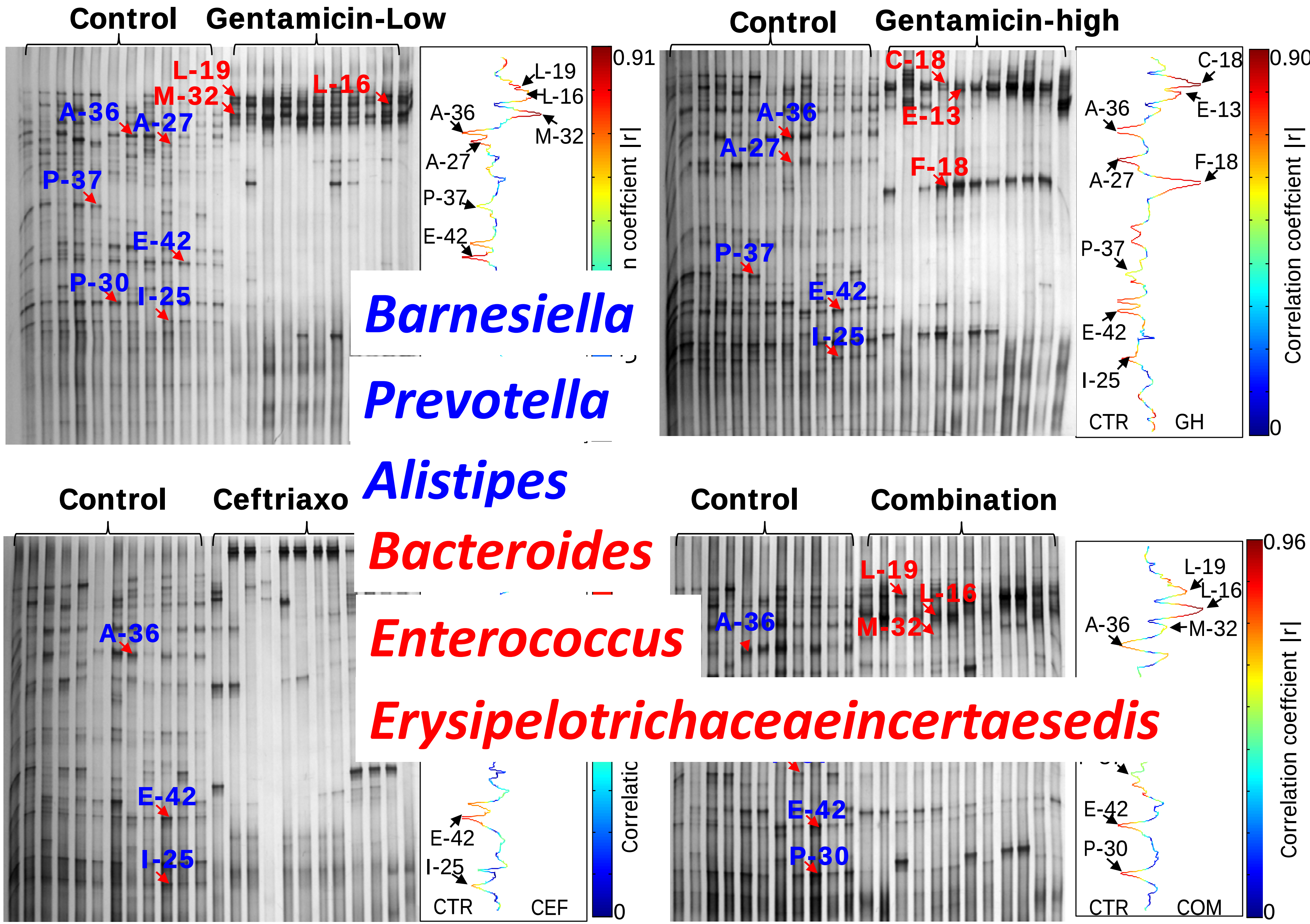
analyzed with a non-parametric Wilcox analysis.

Bacteriology culture values ranged from 0 to 4.

Adams *et al. BMC Gastroenterology* 2011, **11**:22
http://www.biomedcentral.com/1471-230X/11/22

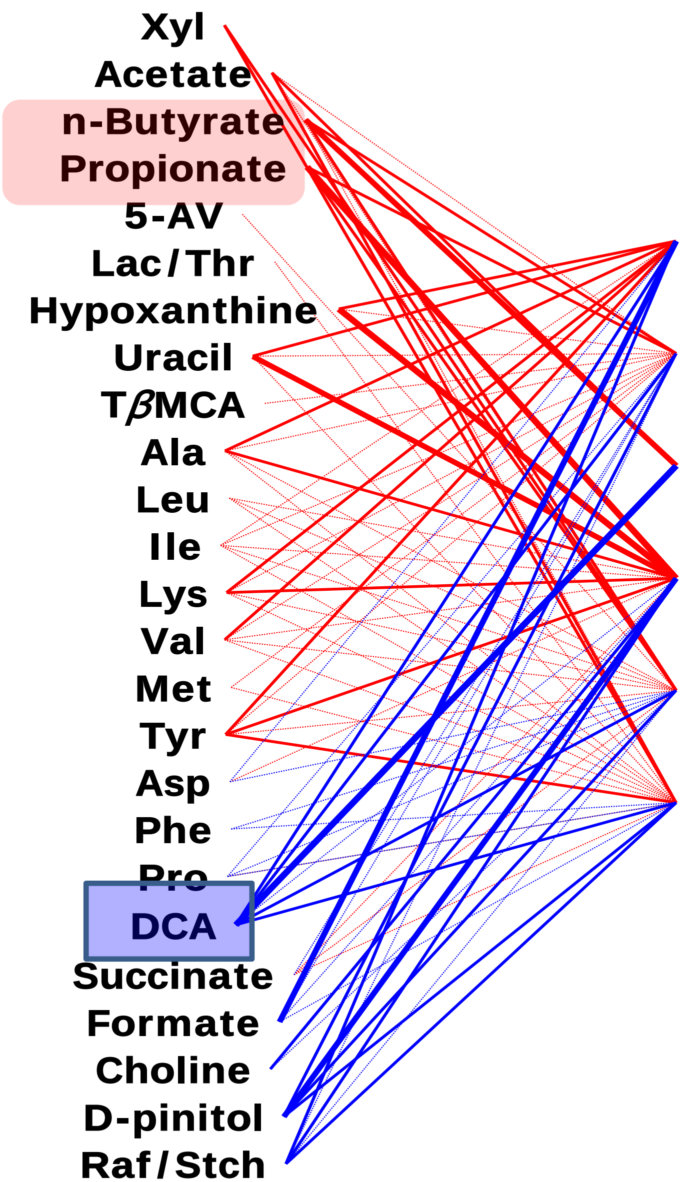
# Two side of coin-short chain fatty acids

- Increase
  - obesity and diabetes
  - Fatty liver
- Decrease
  - Inflammatory bowel disease
  - Neurodegenerative disease

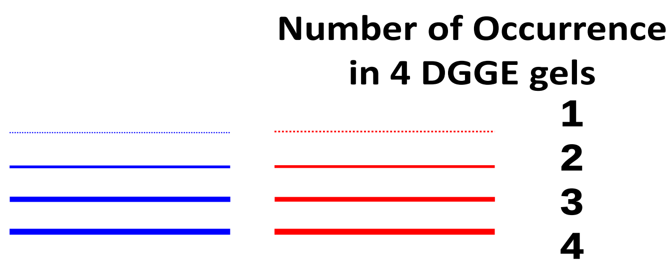


Control
Gentamicin-Low
Gentamicin-high
Ceftriaxo
Combination
L-19
M-32
L-16
A-36
A-27
P-37
E-42
P-30
I-25
C-18
E-13
F-18
CTR
GH
CEF
COM
0.91
0.90
0.96
0
Correlation coeffcient |r|
Barnesiella
Prevotella
Alistipes
Bacteroides
Enterococcus
Erysipelotrichaceaeincertaesedis

# Correlation between microbes and metabolites

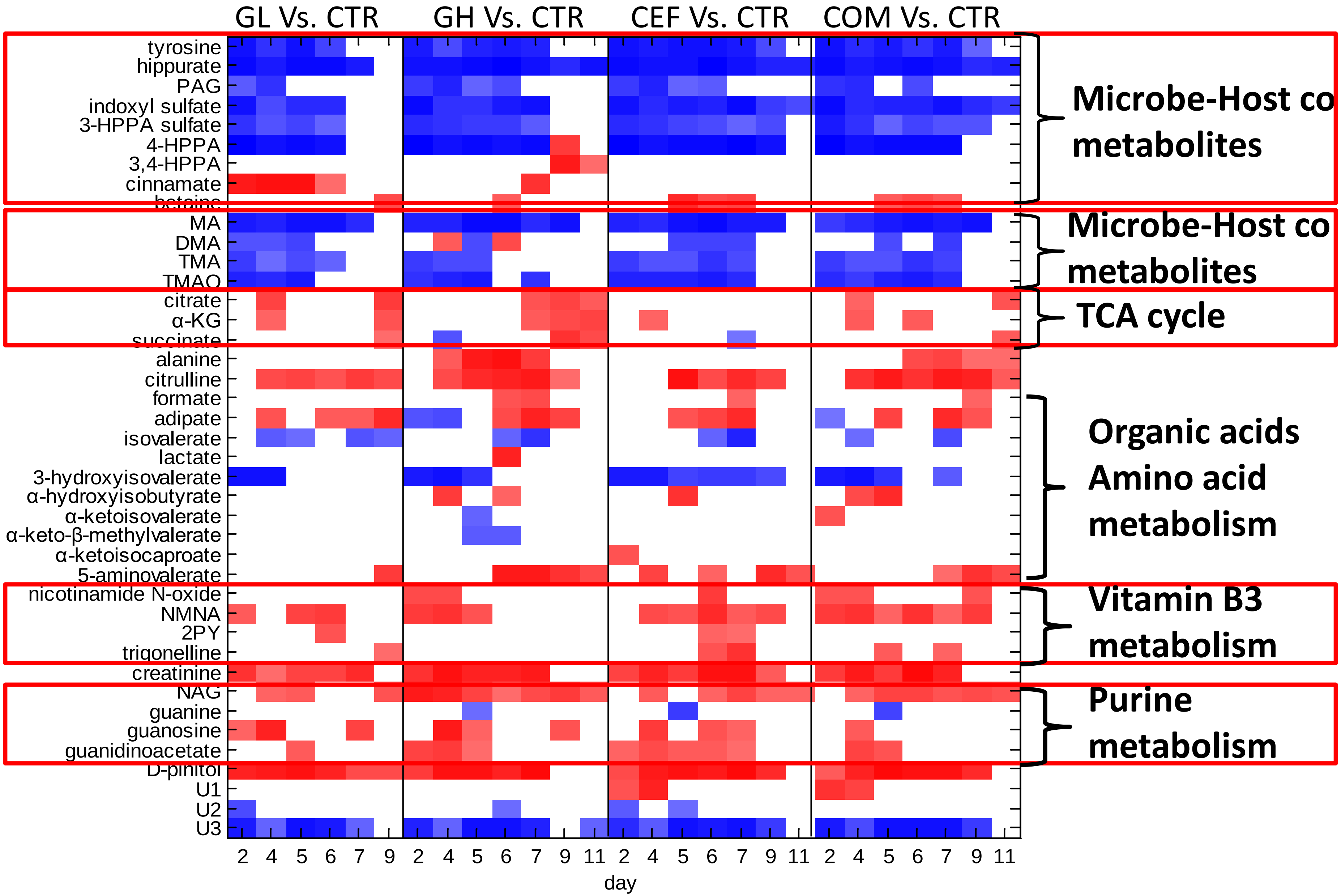


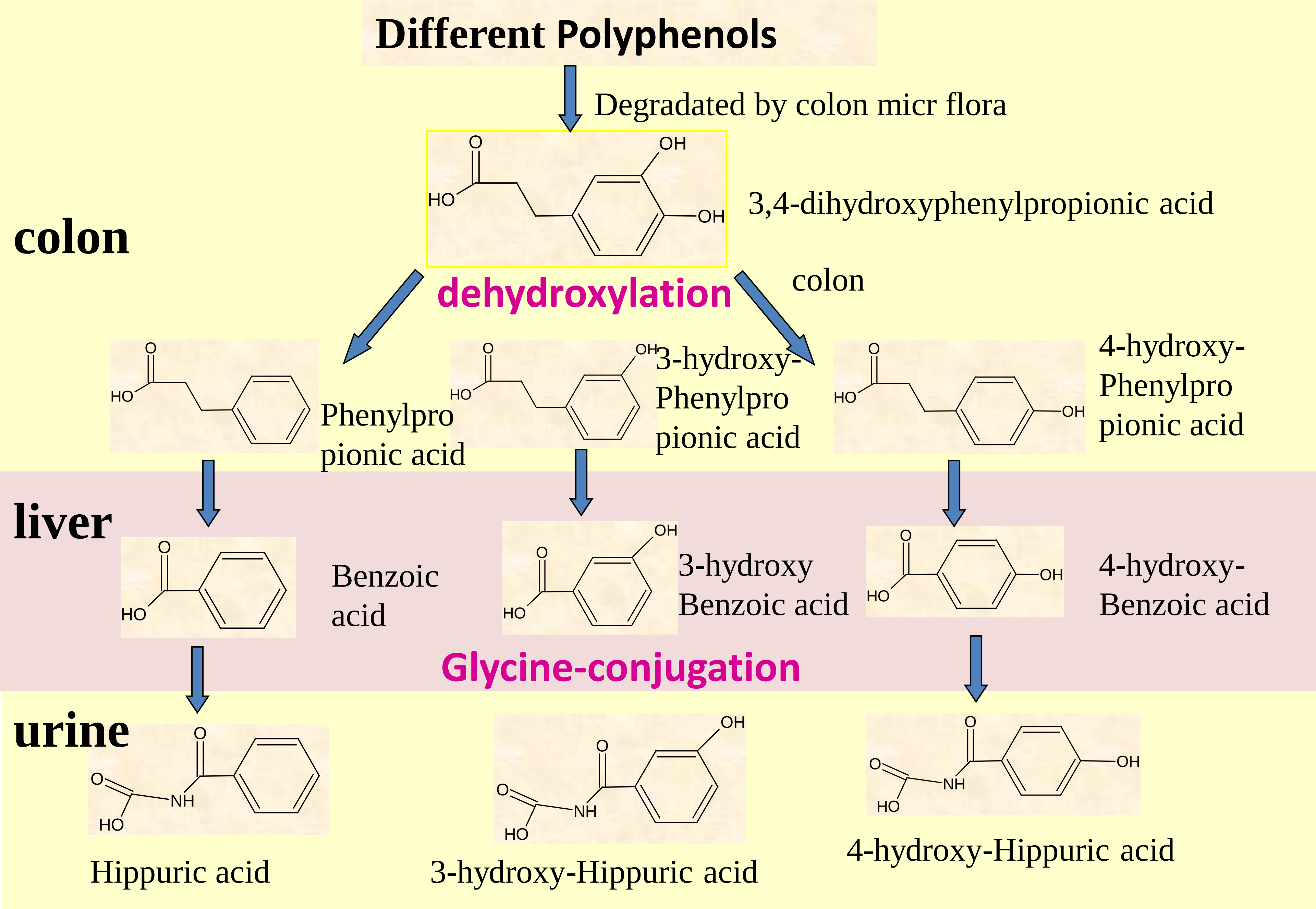

| DGGE band | genus | species | S_ab score |
|---|---|---|---|
| A-36 | *Prevotella* | uncultured bacterium | 1.000 |
| A-27 | *Alistipes* | uncultured bacterium | 0.885 |
| P-37 | *Barnesiella* | uncultured bacterium | 1.000 |
| E-42 | *Barnesiella* | uncultured bacterium | 1.000 |
| P-30 | *Barnesiella* | uncultured bacterium | 1.000 |
| I-25 | *Barnesiella* | uncultured bacterium | 1.000 |




Zhao et al. J. Proteome Res., 12:2987-2999，2013

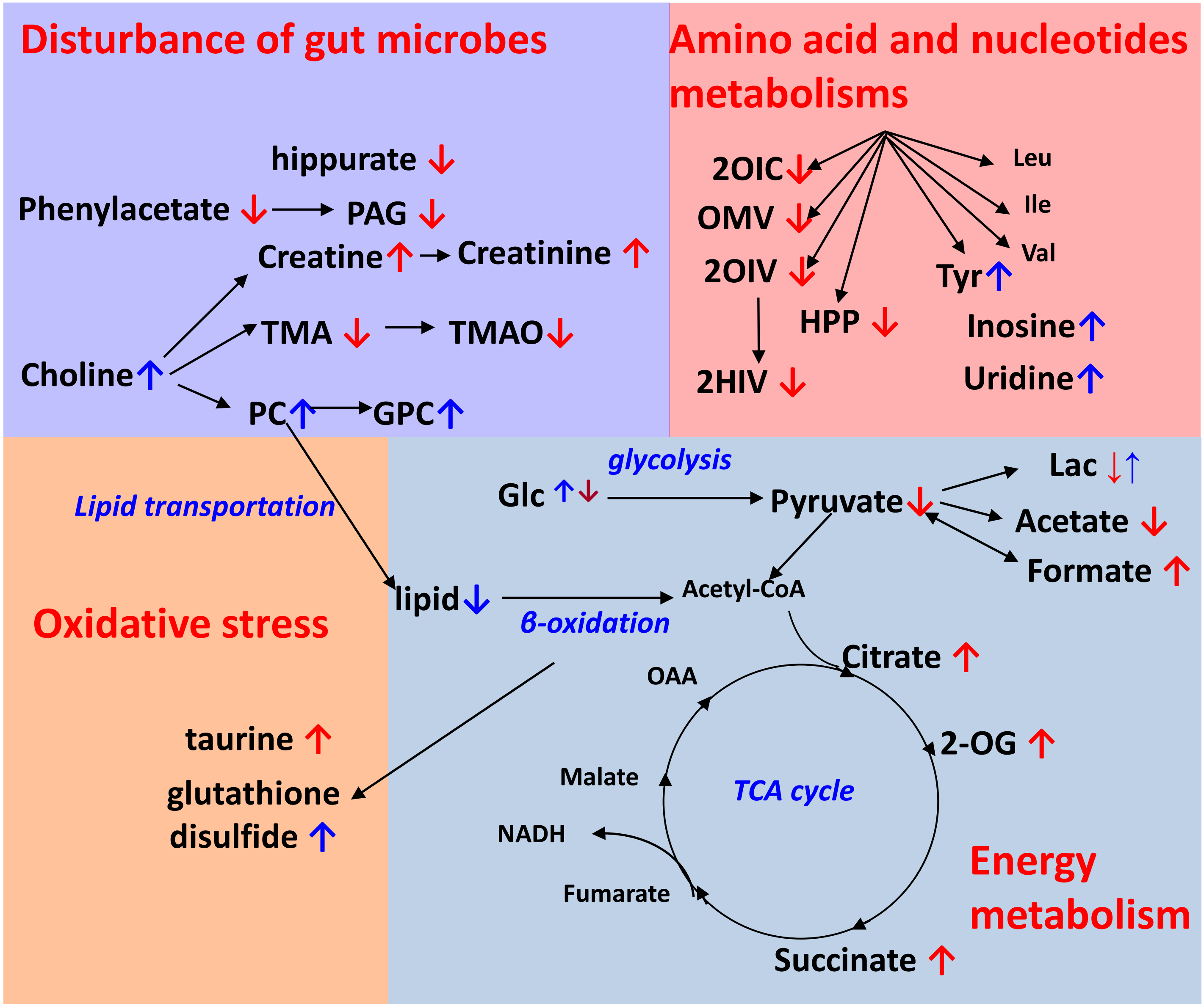
# Antibiotics treatments also caused other metabolic changes





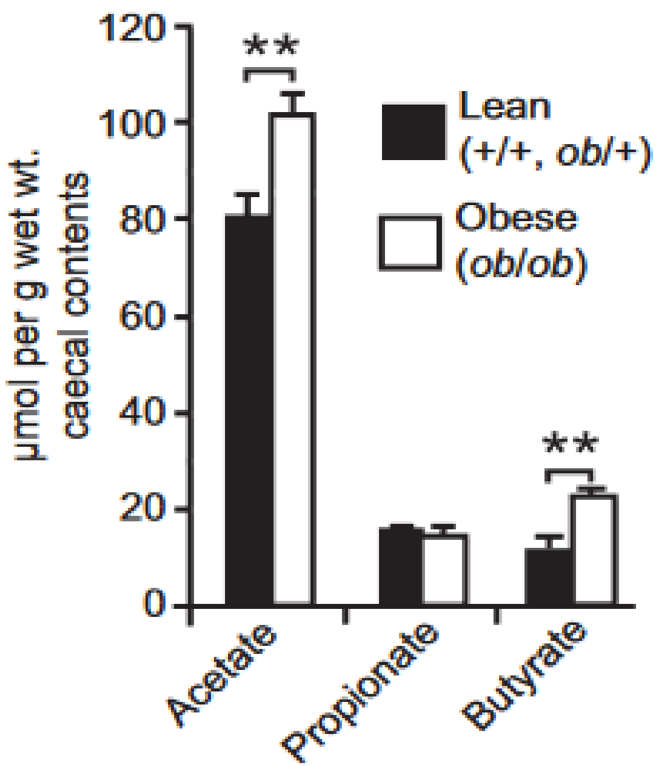

Free radical biology &medicine, Vol. 33, pp 220-235

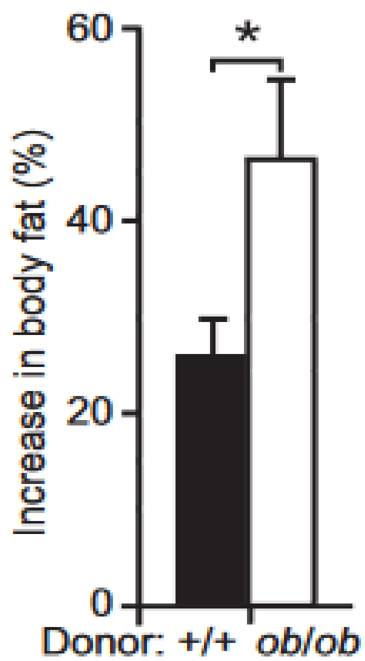
# Mequindox induces metabolic changes in mice




Zhao, J Proteome Res, 2011, 10, 5183-6190

# Microbes of obesity can be transferred

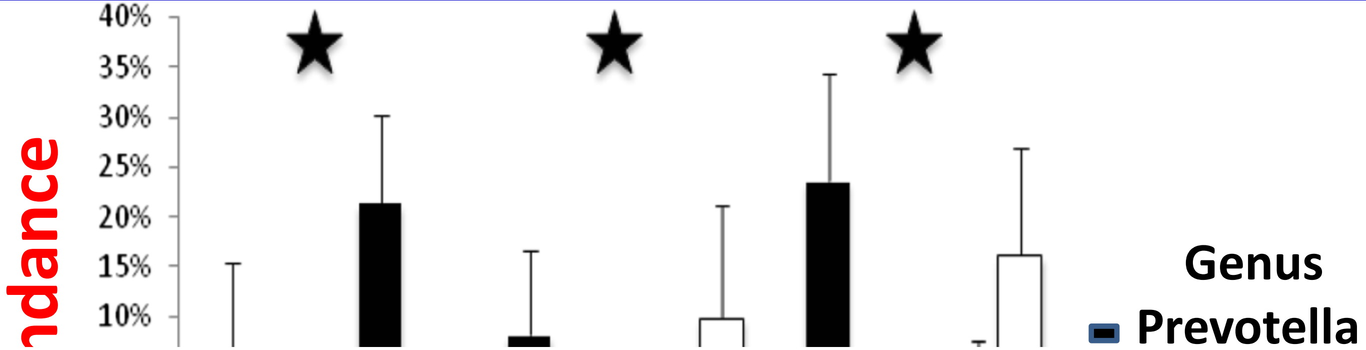


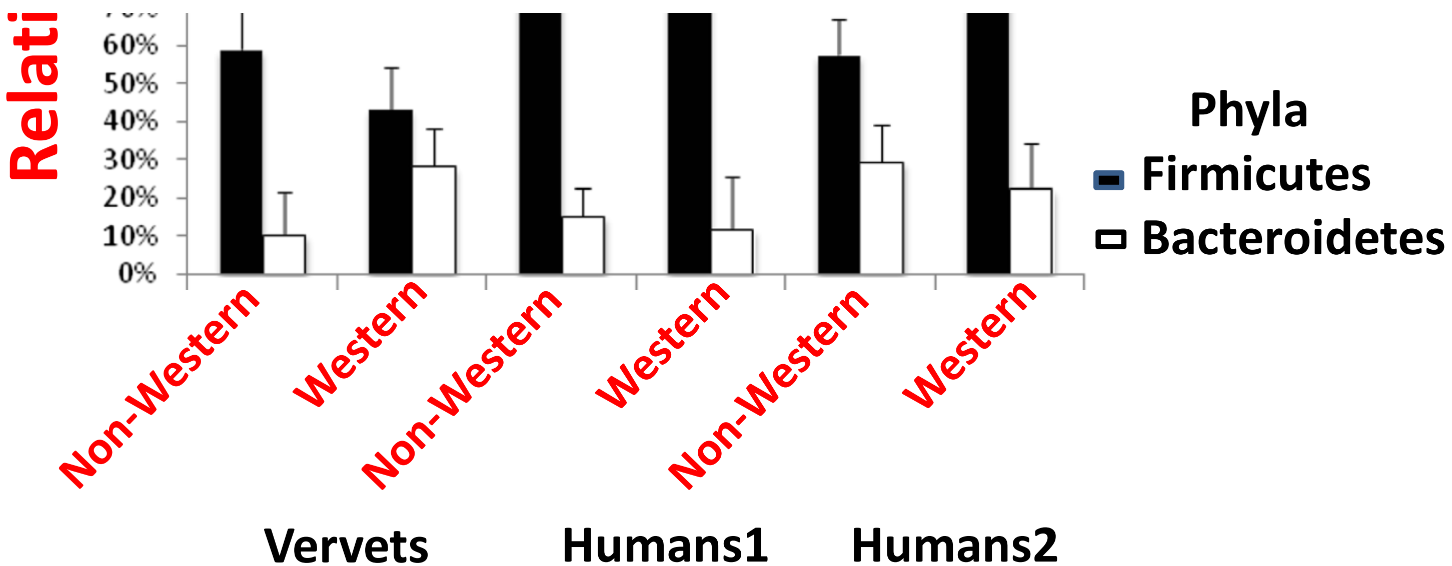

- **Feces from ob/ob can make mice fatter**
- **Fatter mice harvest more energy from food**

P. Turnbaugh, et al. (2006) Nature, 444: 1027-1031

# High caloric intake modulates gut microbes in primates

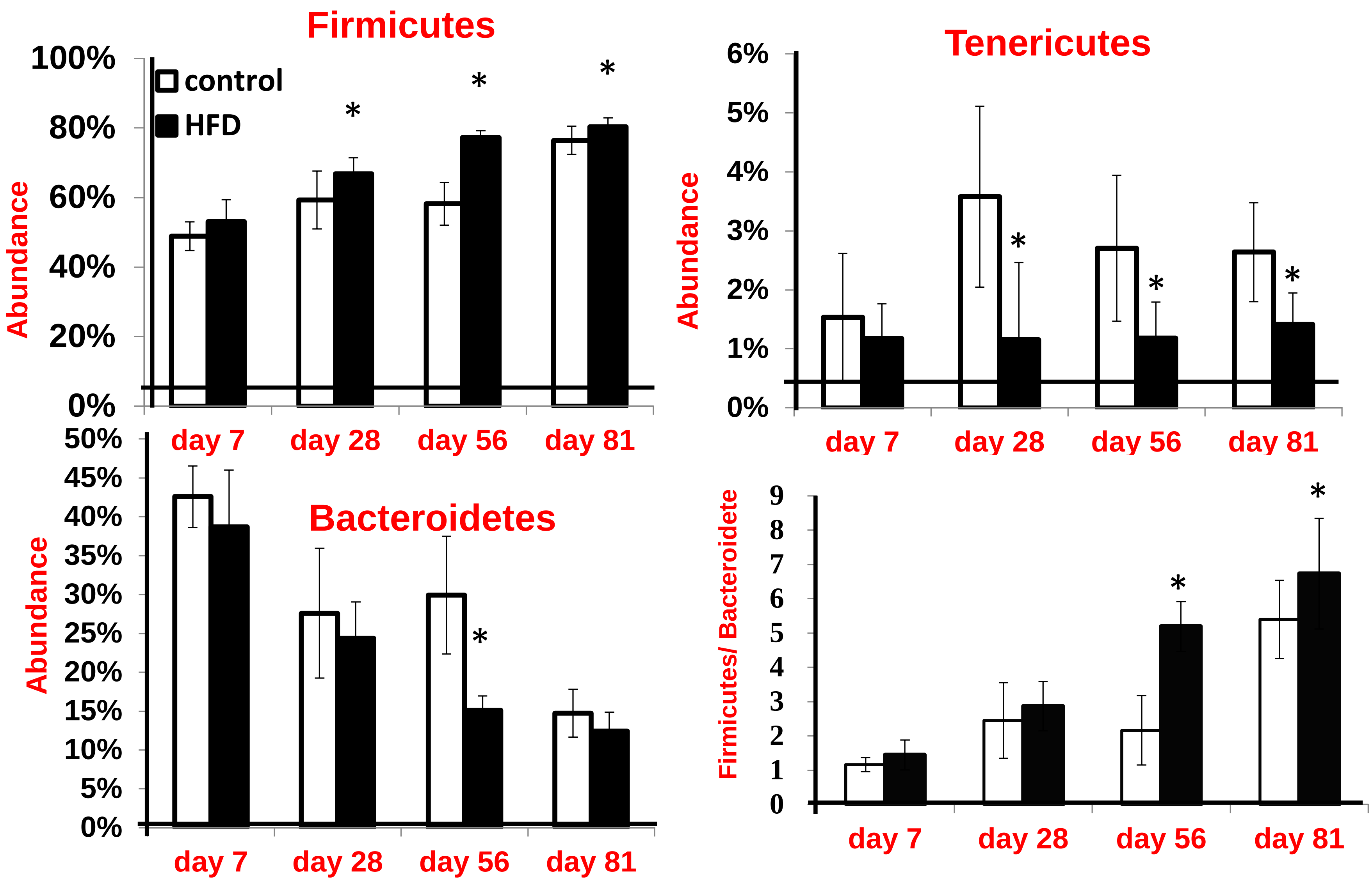



**Increased levels of Bacteroides is similar to the effects of antibiotics treatment**




Amato, Microbiome, 2015, 3, 53

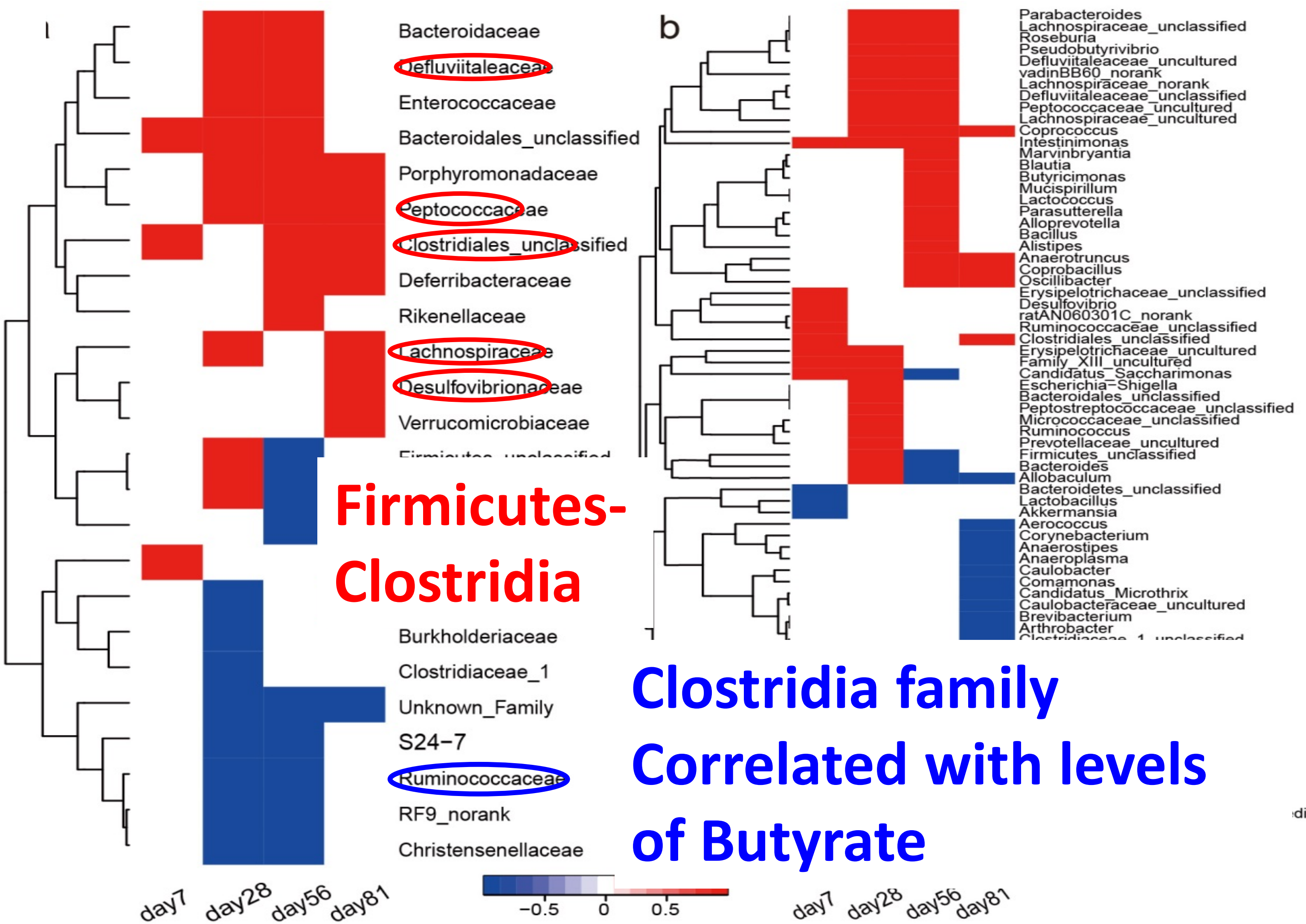
# High caloric intake modulates gut microbes in rats




H. Lin, et al, Scientific Reports 6 (2016)

# High caloric intake modulates gut microbes

**Family level** **Genus level**

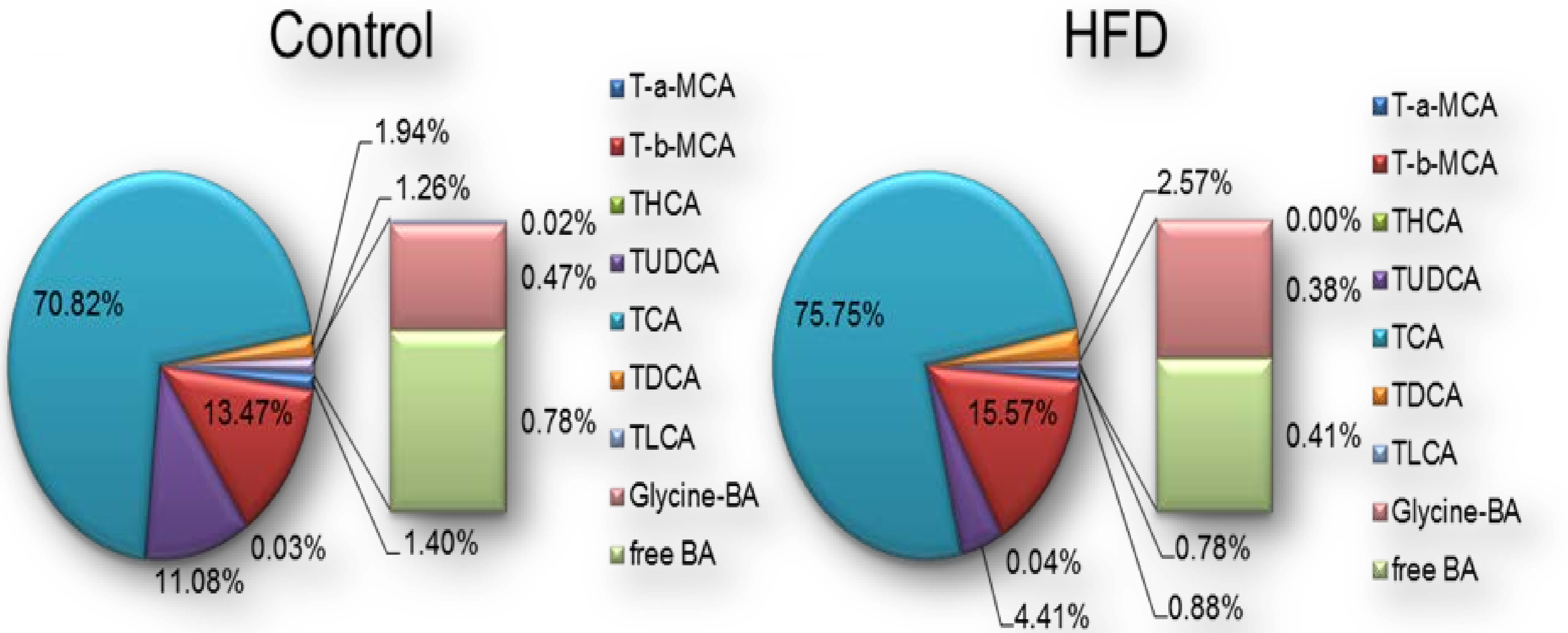



**Firmicutes-Clostridia**

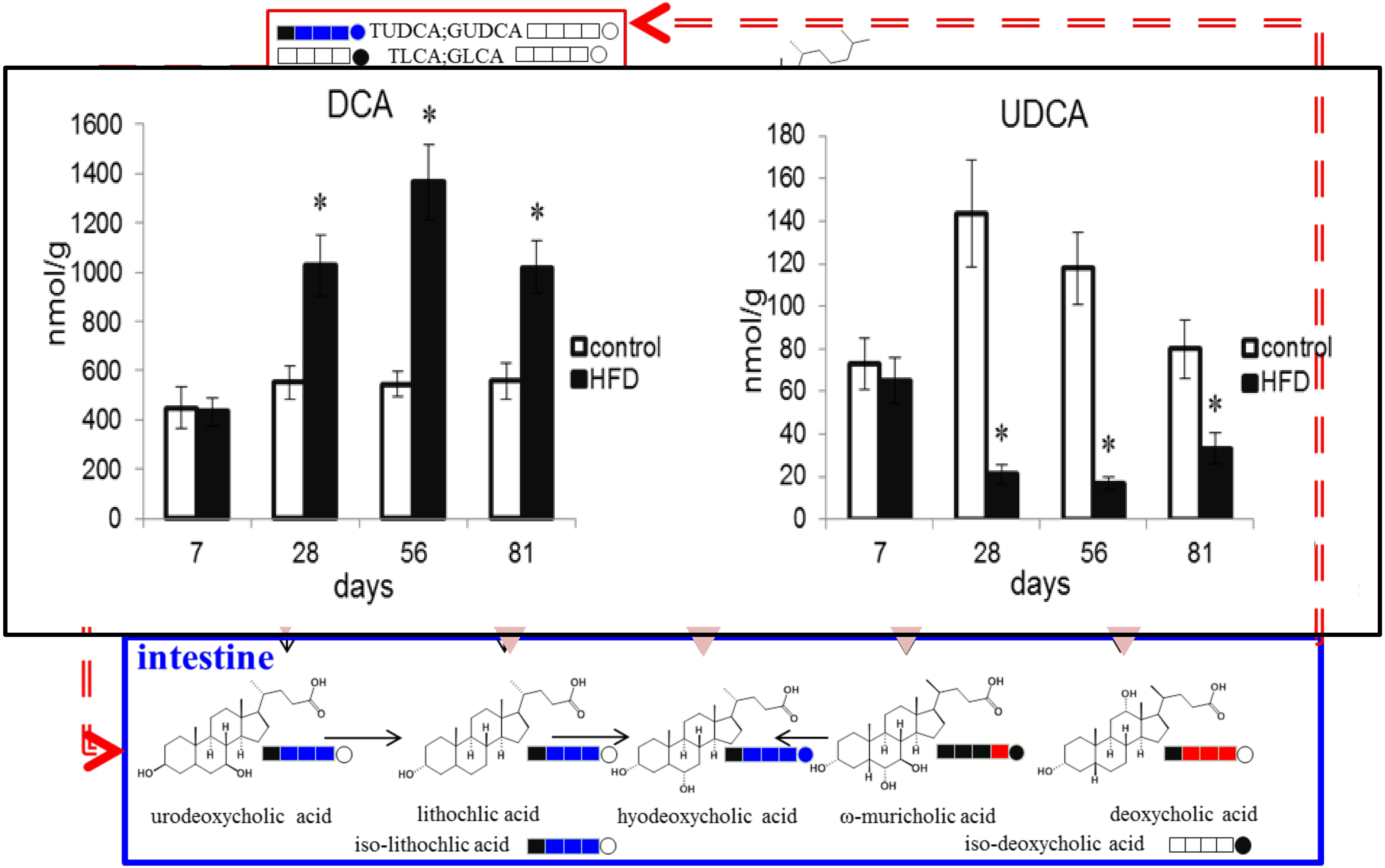
**Clostridia family Correlated with levels of Butyrate**

**H. Lin, et al, Scientific Reports 6 (2016)**

# High caloric intake increased bile acids production in liver of rats



# gut microbes shape host metabolism



# High fat diet-gut microbes-DCA-colon cancer

HFD-increased levels of DCA

colon cancer associated secondary bile acids

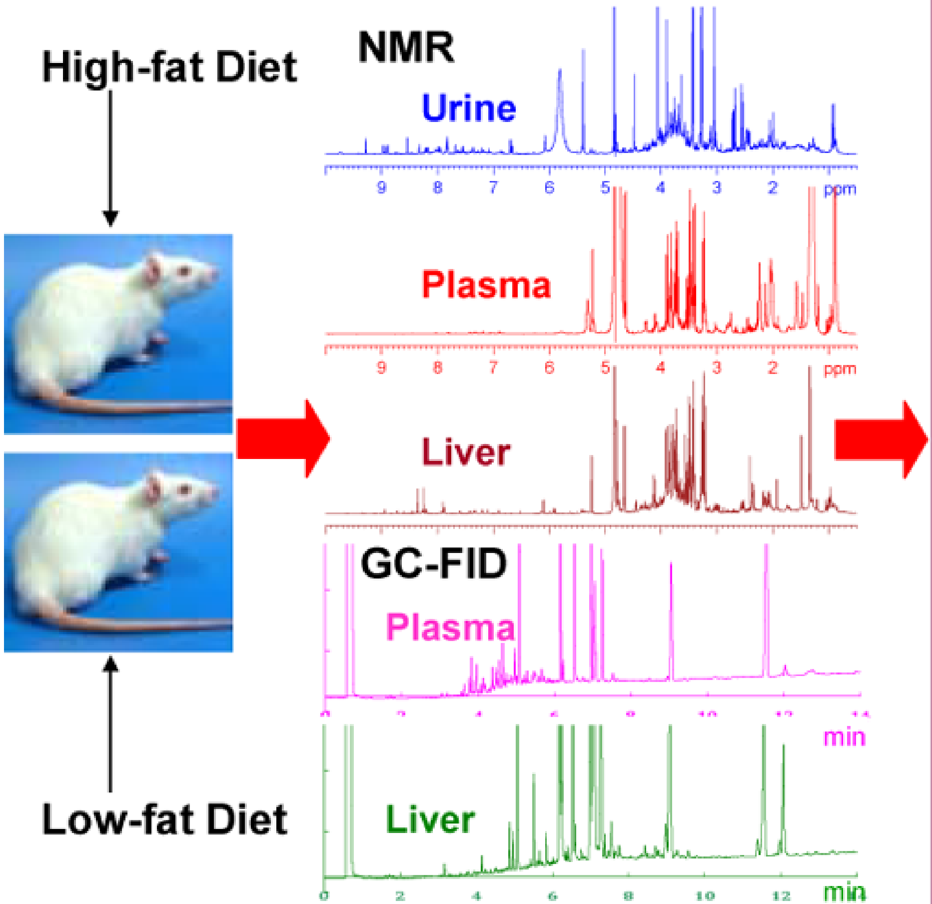
*Diet Induced Changes in the Colonic Environment and Colorectal Cancer*

**Ursodeoxycholic Acid (UDCA) Can Inhibit Deoxycholic Acid (DCA)-induced Apoptosis via Modulation of EGFR/Raf-1/ERK Signaling in Human Colon Cancer Cells[1,2]**

Eunok Im and Jesse D. Martinez[3]

*Arizona Cancer Center, Department of Radiation Oncology, University of Arizona, Tucson, AZ 85724*

# High fat intake (81 days) modulates other metabolic pathways

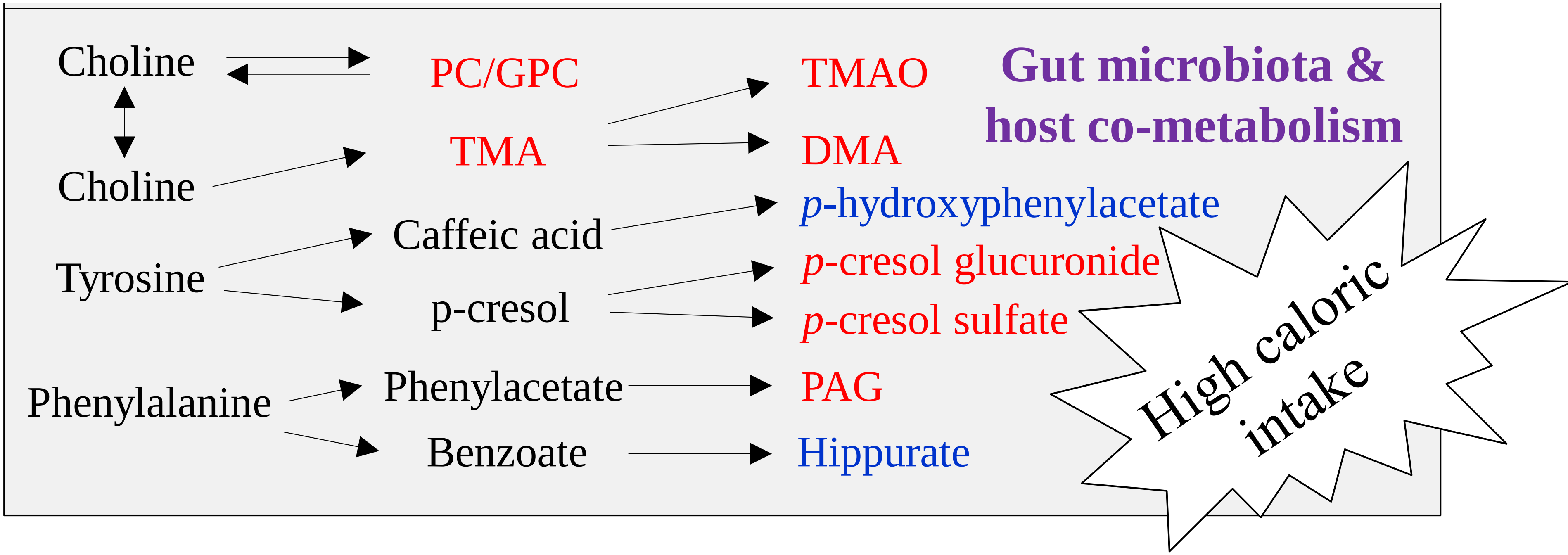



## Altered Metabolism

- Lipogenesis
- Glucose-fatty acid cycle
- β-oxidation and oxidative stress
- Choline metabolism
- Gut microbiota functions
- Purine and amino acid Metabolism
- Metabolism of B Vitamins

An, J Proteome Res, 2013, 12, 3755-3768

# High fat intake (74 weeks) modulates microbes associated metabolites in mice




J. Wu, J Proteome Res, 2016, 15, 2299-2308

# Summary

## Action of gut microbes

- Short chain fatty acids
- Choline metabolism
- Bile acids metabolism
- Polyphenols

# Acknowledgements

Prof Huiru Tang
Dr. Yanpeng An

Prof. J. Nicholson
Prof. E. Holmes
Dr. J. Swann

Prof. Linong Ji
Dr. Xiuying Zhang

Dr. Junfang Wu;
Dr. Xiuju Zhao;
Dr. Ying Zhao;
Dr. Hong. Lin

Financial supports

CAS, NSFC, MOST