



上海交通大学
Shanghai Jiao Tong University



Top-down vs. Bottom-up

Gut Microbiota and Whole-body Systems Biology 肠道菌群与人体系统生物学

Liping Zhao

Shanghai Center for Systems Biomedicine

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University, Shanghai 200240, China

中国上海市东川路800号上海交通大学生物楼3 - 517 赵立平



“模糊的”整体

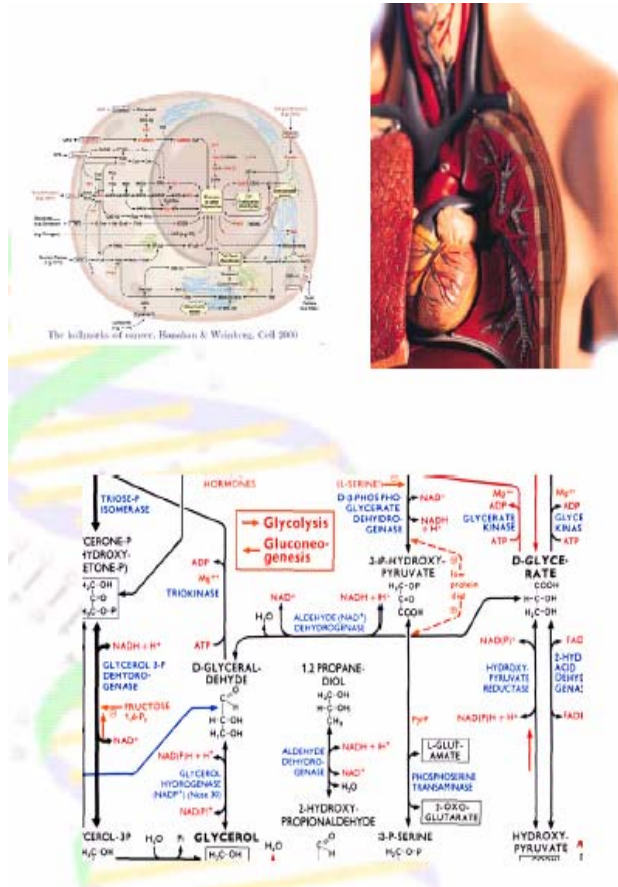
- The four diagnostic techniques “四诊”
 - 望、闻、问、切
- The eight guiding principles for differentiation of syndromes “八纲辨证”
 - 表里
 - 寒热
 - 虚实
 - 阴阳

感官测量 经验判断

Holistic but empirical



从基因的角度解释和防治疾病的分子医学 Gene-centric, molecular medicine



精细的局部
Molecular yet local

- 基因序列多样性与疾病易感性的关系
- 基因序列多样性与药物敏感性的关系
- 基因表达特性与药物代谢机理
- 基因表达特性与疾病发展过程
-

定量测定 模式识别

Molecular detail at cellular level
but fragmentary
at whole body level



TCM vs. Western Medicine

- Diseased man vs. man' s disease
- 病的人与人的病
- Stratification of patients vs. classification of diseases
- 病人分类与疾病分型
- Top-down vs. bottom-up
- 自上而下与自下而上
- Global vs. local
- 整体到局部与局部到整体
- Intact person vs. Genes
- 完整的人体与基因

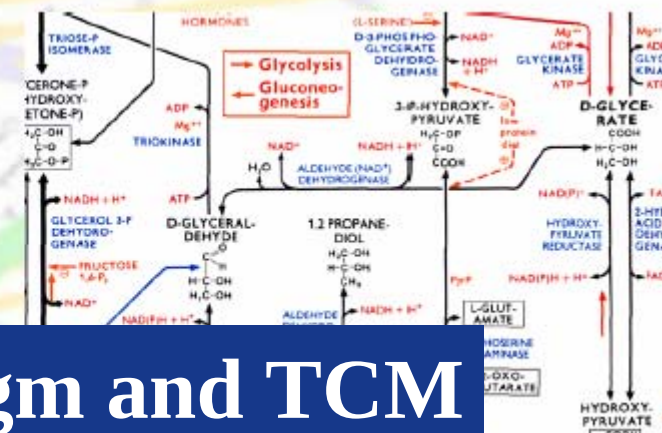
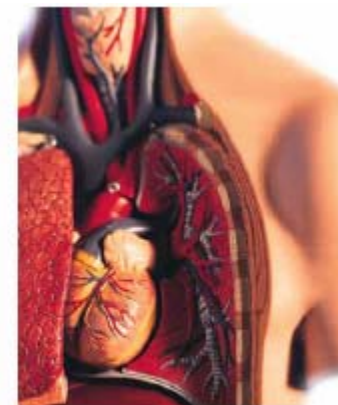
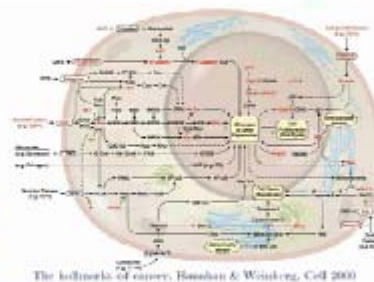




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Complex systems share the same nature 复杂系统在本质上都是相似的



Engineering paradigm and TCM 工程学思维模式与中医理论

Tools for understanding complex engineering systems can be applied in biomedicine



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Complex systems share the same nature
复杂系统在本质上都是相似的

“To understand the whole,
One must study the whole”
要理解整体就必须研究整体

4, 涌现特性
Emergent properties

Engineering paradigm and TCM
工程学思维模式与中医理论

Tools for understanding complex engineering systems can be applied in biomedicine





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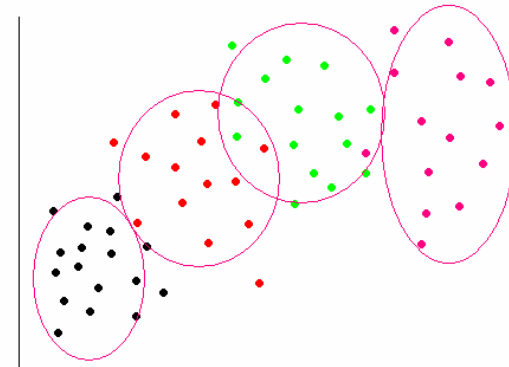


涌现特性测量与复杂系统分类和监测

Classification and monitoring of complex systems based on measurements of emergent functions

Systems states and state space models

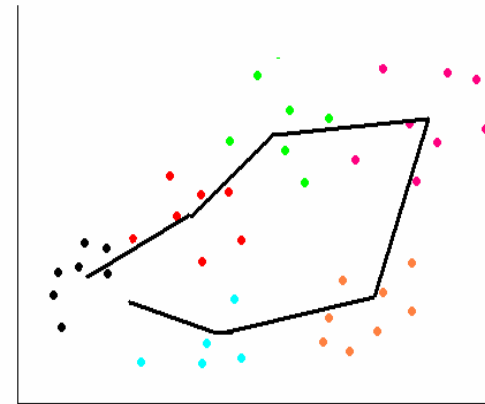
- Structural state 结构状态
- Functional state 功能状态



State space model
状态空间模型

System trajectory analysis

- Attractors 吸引子
- Initial conditions 起始条件
- Disturbances 扰动



System trajectory analysis
系统轨迹分析



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结构健康监测 Structural Health Monitoring





Changes in vibration, noise and exhaust gas for engine health monitoring

AIAA 1st Intelligent Systems Technical Conference
20 - 22 September 2004, Chicago, Illinois

AIAA 2004-6461

Development of an Information Fusion System for Engine Diagnostics and Health Management

Allan J Volponi

Pratt & Whitney, East Hartford, CT 06108

Tom Brotherton

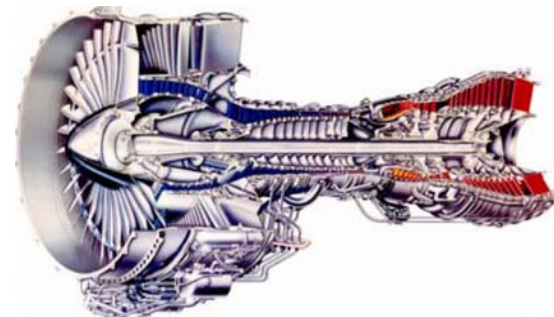
Intelligent Automation Corp., Poway, CA 92064

Robert Luppold

Luppold & Associates, West Newton, PA 15089



Figure 1 C-17 Globemaster



振动、噪声和尾气的模式变化与发动机健康监测



Classification and identification of complex systems based on the measurement of their emergent functions

基于涌现特性测量的复杂系统的 精细分类与鉴定

Classification in an unsupervised learning mode
with no prior knowledge required
无监督的学习分类模式

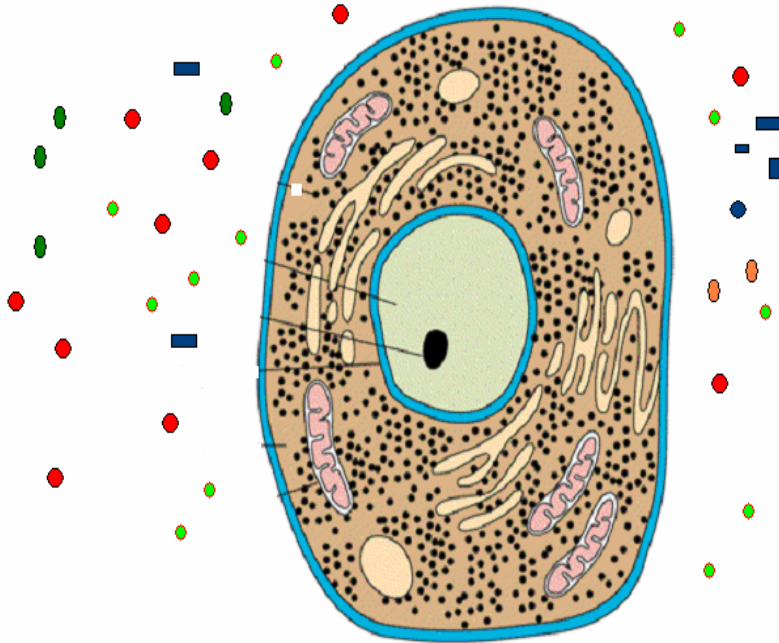


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Emergent functions of the cell

细胞的涌现特性



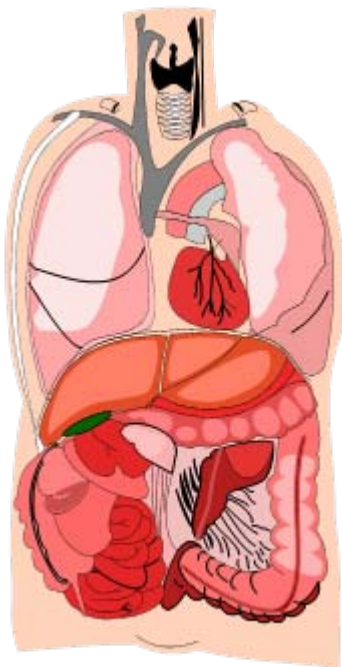
-  **Secretome**-extracellular proteins
分泌组 - 胞外蛋白质全谱
-  **Metabonome**-extracellular metabolites
代谢组 - 胞外代谢物全谱
-  Vibration 振动
-  Noise 噪声
-  Exhaust Gas 尾气

Nicholson 2004



Emergent functions of the human body

人体的涌现特性



Metabonome
代谢组
Metagenome
元基因组
Secretome
分泌组



- Urine-metabolites
尿液代谢物谱
- Feces-bacteria
粪便细菌谱
- Blood-proteins
血液蛋白质谱

- Vibration 振动
- Noise 噪声
- Exhaust Gas 尾气

人体系统生物学与健康测量

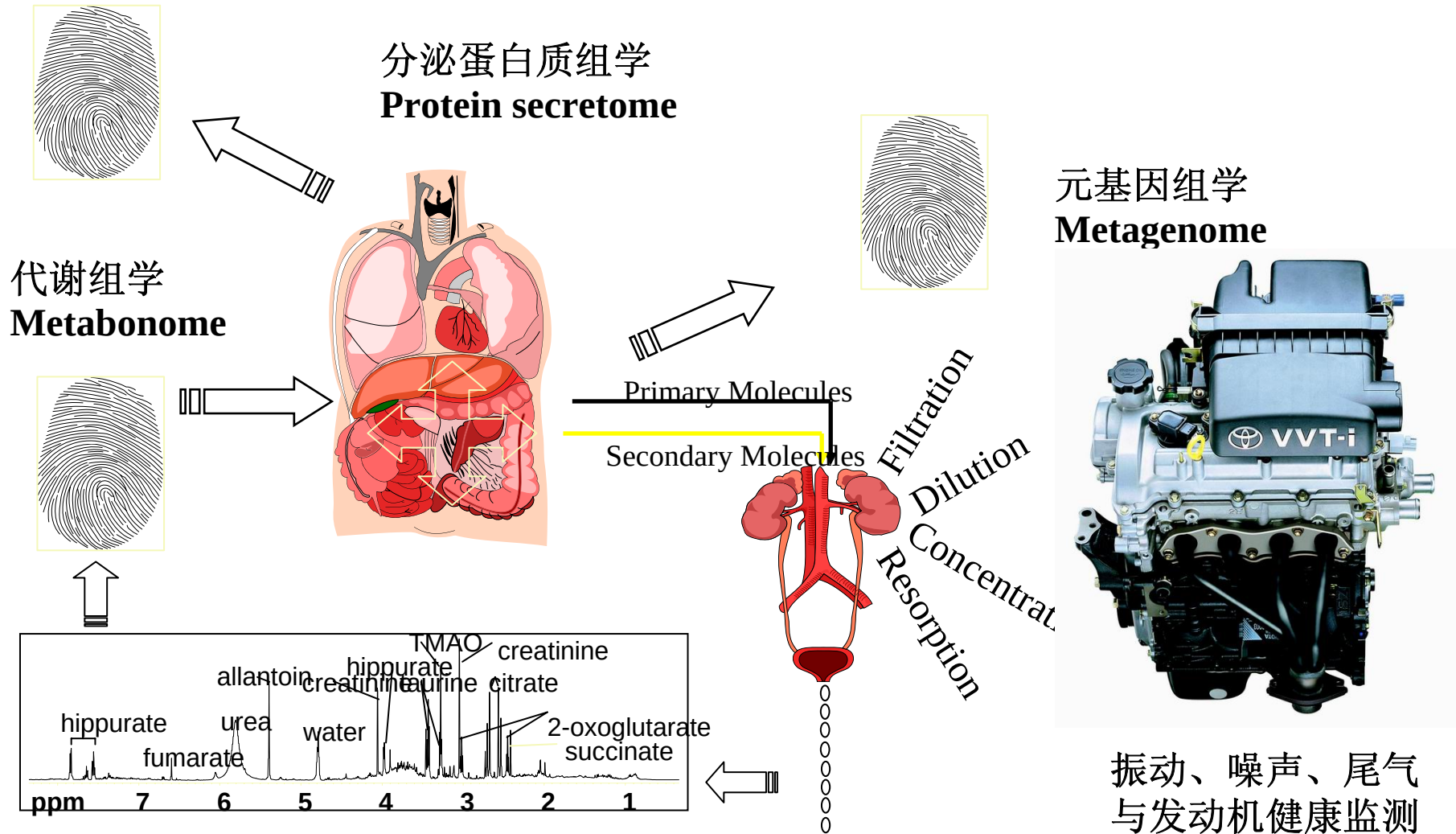
(Whole-body systems biology and health assessment)

- 人体系统生物学通过在人体水平测定基因与环境互作的结果来准确评估和监测人体的健康
- Health assessment and monitoring based on measurements of results of gene-environment interactions at the whole-body level
- 具有下列特征Essential criteria :
 - 非破坏性测量，可直接用于人体
 - Non-invasive
 - 整体测量，反映全身的健康状况
 - Global
 - 高通量、低成本可实现大样本人群的动态监控
 - Dynamic, low-cost, high throughput
 - 以核酸、蛋白和代谢物等生物分子为测定对象
 - Molecular-based
 - 非靶向测定，通过“全谱扫描”和“盲分类”可以监测任何类型的健康变化
 - Non-targeted
 - 数字化测量，可实现高度信息化
 - Digital, quantitative, highly reproducible

人体健康的分子测量

Molecular assessment of human health at the whole-body level

——人体健康状况的多参数、多指标评估





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Systems approaches for quantitative assessment and monitoring of human health 用系统定量的方法进行 人体健康状况的评价与监测

Molecular Profiling and Covariation Analysis
全谱分子扫描技术与模式识别



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Gut Microbiota and Whole-body Systems Biology

Liping Zhao

Shanghai Center for Systems Biomedicine
School of Life Science and Biotechnology
Shanghai Jiao Tong University





New view on human body The Superorganism Concept *

**Joshua Lederberg*



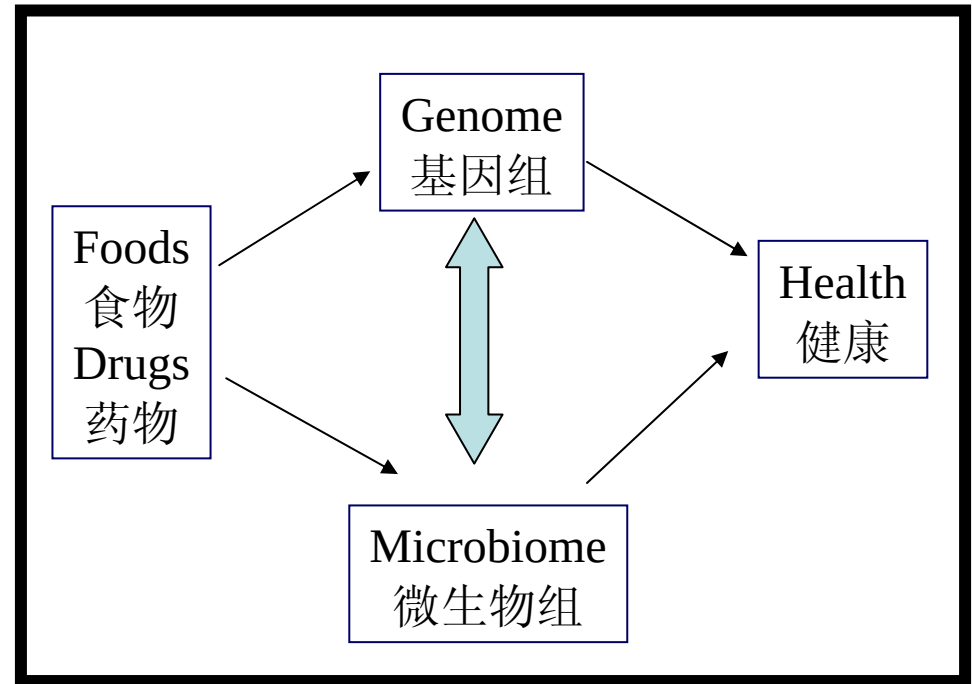
Cell composition of human body

- 10% human cells
- 90% bacterial cells



Gene composition of human body

- Human genome (25,000 genes)
 - Karyome
 - Mitochondrome
- Microbiome
 - 1000 species
 - 1 million genes
 - Diverse and active metabolism



Human microbiome-
the second genome acquired after birth

微生物组—人后天获得的第二个基因组



New view on human body The Superorganism Concept *



Cell composition of human body

- 10% human cells
- 90% bacterial cells

**Joshua Lederberg*



Gene composition of

全基因组关联分析要包括肠道菌群的基因
Whole-genome association studies should
Include our microbiome

- Microbiome
 - 1000 species
 - 1 million genes
 - Diverse and active metabolism

Genome

Microbiome
微生物组

Human microbiome-
the second genome acquired after birth

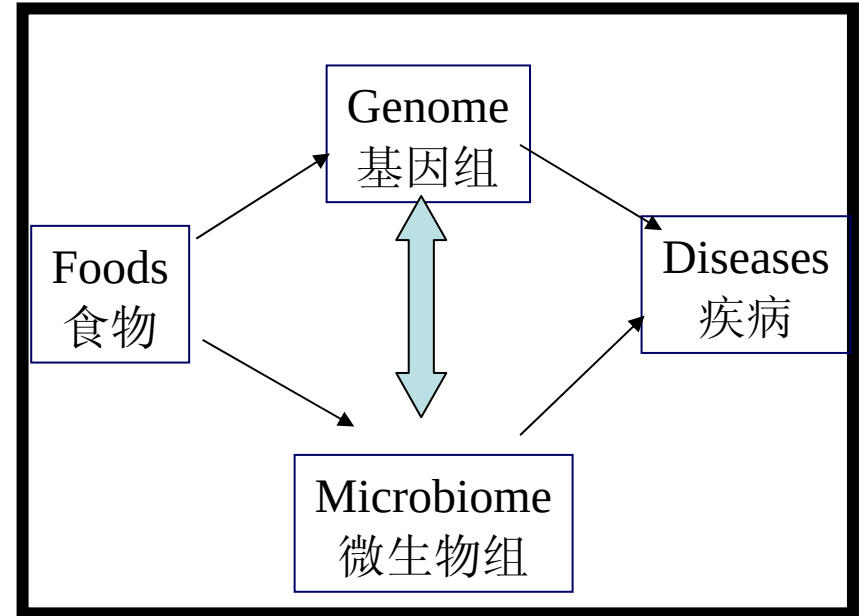
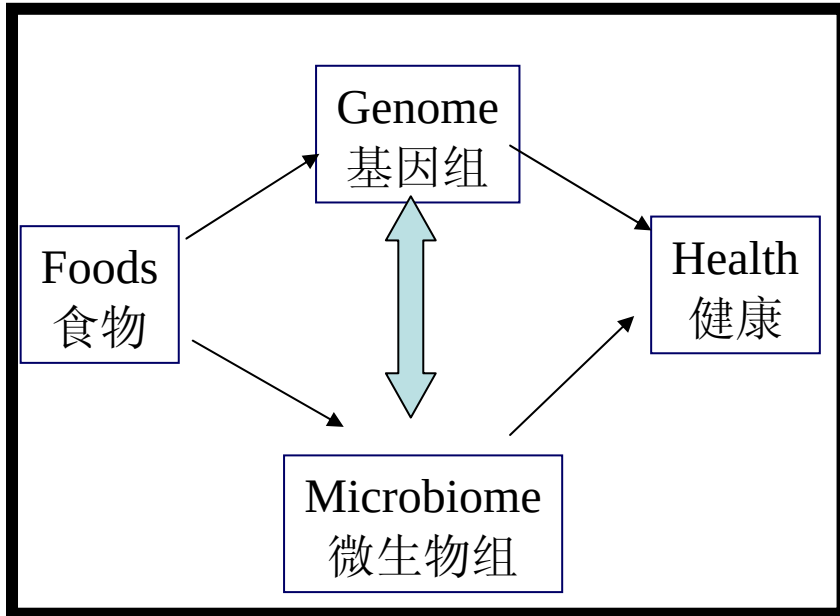
微生物组—人后天获得的第二个基因组



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Modulation of the second genome in the Superorganism



Partner for health or Pathogen for diseases?

TCM works primarily via modulation of gut microbiota

肠道菌群其实一直就是中医药的主要作用靶点

PERSPECTIVES

OPINION

Gut microbiota: a potential new territory for drug targeting

Wei Jia, Houkai Li, Liping Zhao and Jeremy K. Nicholson

Abstract | The significant involvement of the gut microbiota in human health and disease suggests that manipulation of commensal microbial composition through combinations of antibiotics, probiotics and prebiotics could be a novel therapeutic approach. A systems perspective is needed to help understand the complex host–bacteria interactions and their association with pathophysiological phenotypes so that alterations in the composition of the gut microbiota in disease states can be reversed. In this article, we describe the therapeutic rationale and potential for targeting the gut microbiota, and discuss strategies and systems-oriented technologies for achieving this goal.

Most current searches for new drugs are generating new insights and opportunities

A microbial organ

The human intestine is more densely populated with microorganisms than any other organ, and is a site where they exert strong influences on human biology. With this in mind, the entire system of the human gut microbiota can be pictured as a ‘microbial organ’ within the intestine, which contributes to diverse mammalian processes including protective functions against pathogens and immune-system modulation, the metabolic function of fermenting non-digestible dietary fibre, and the anaerobic metabolism of peptides and proteins, which results in the recovery of metabolic energy for the host^{10–12}.

The intestinal mucosa is the main interface between the immune system and external environment and therefore has an important role in the host–flora interaction. The commensal microbiota profoundly influences the development of humoral com-

strategies for
prove the pro-
tical industry,
uge investments
urgets and drug
ccess so far.
icle provides
eutic and
of diseases and
gut microbiota,
gut microbiota-



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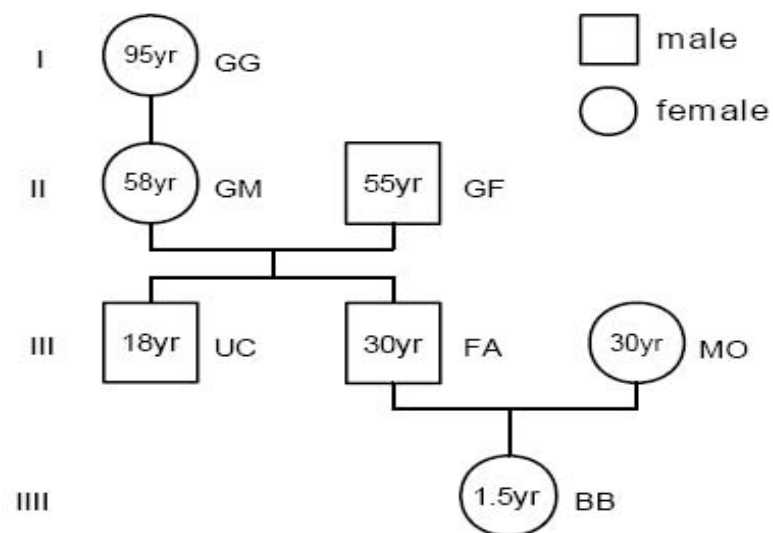


Functional analysis of gut microbiota

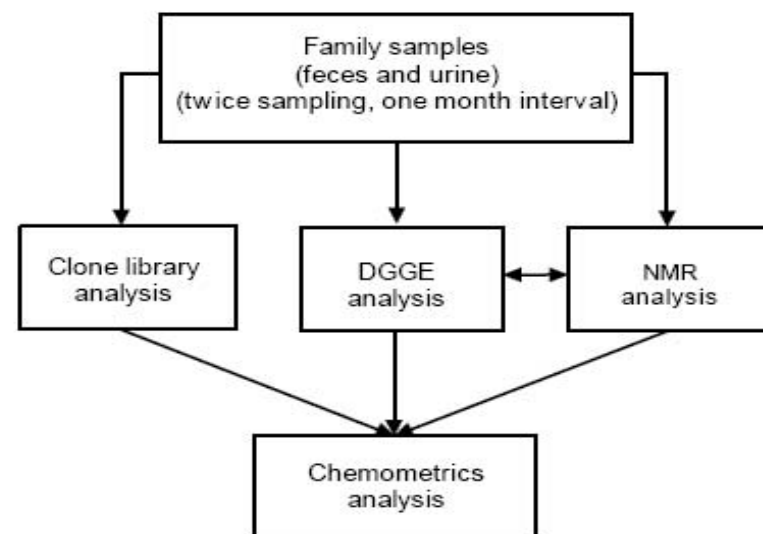
-Co-variation analysis between host
global metabolism and gut microbiota

Li et al. , PNAS

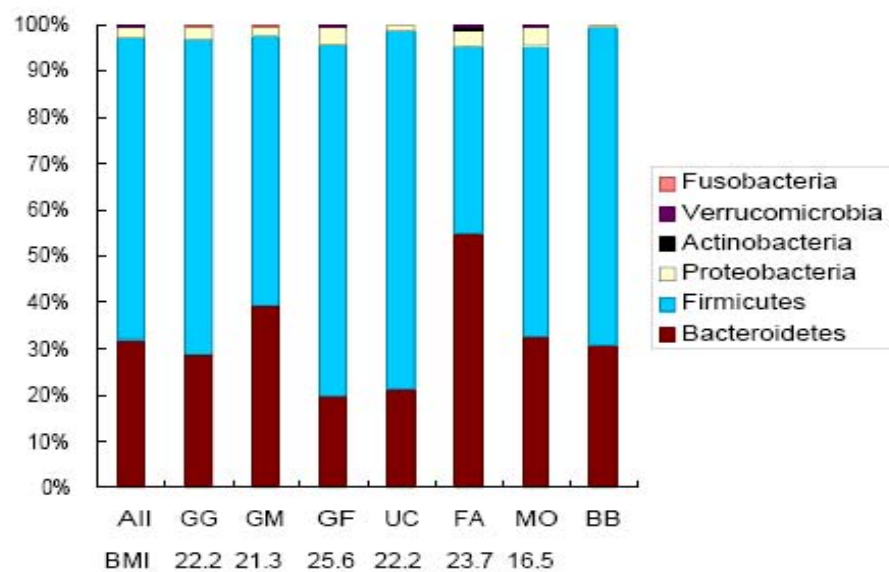
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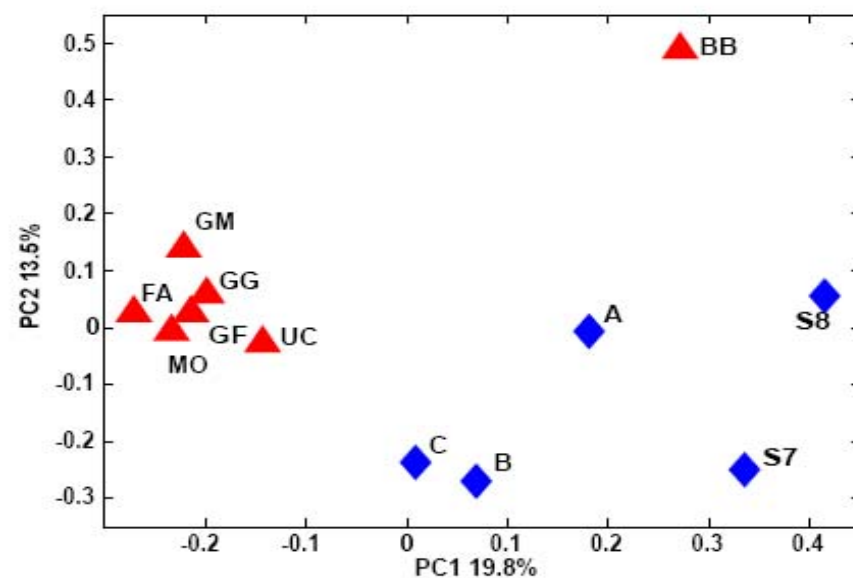
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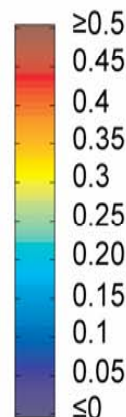
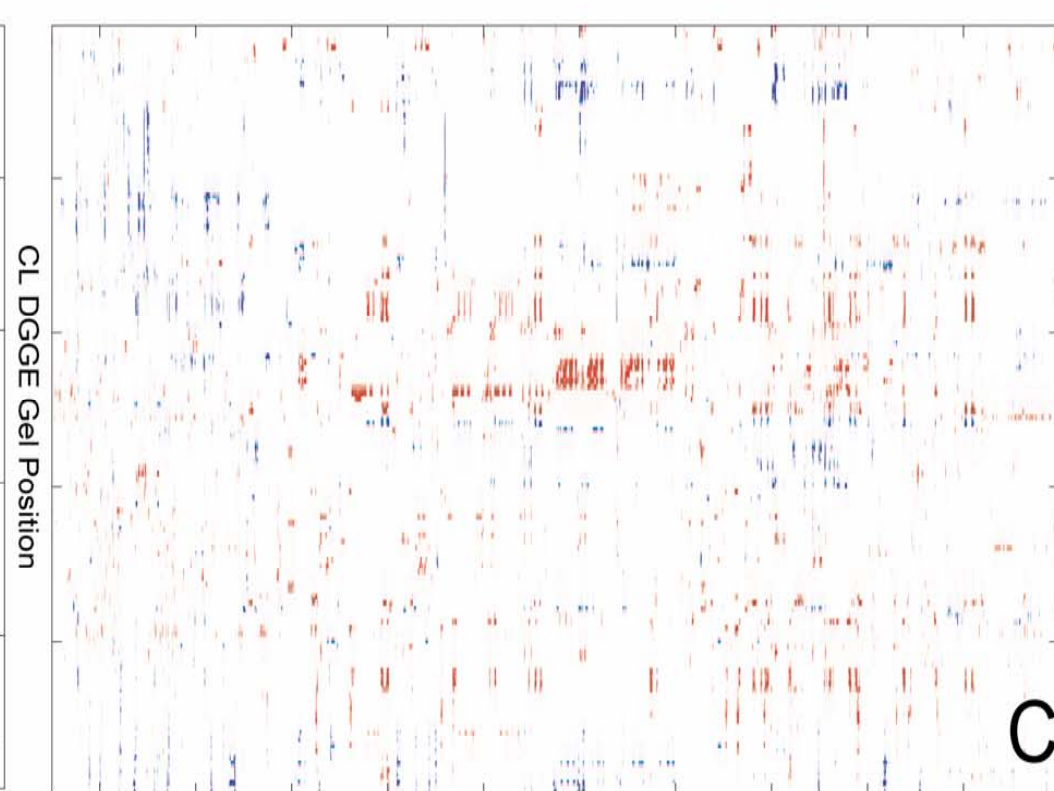
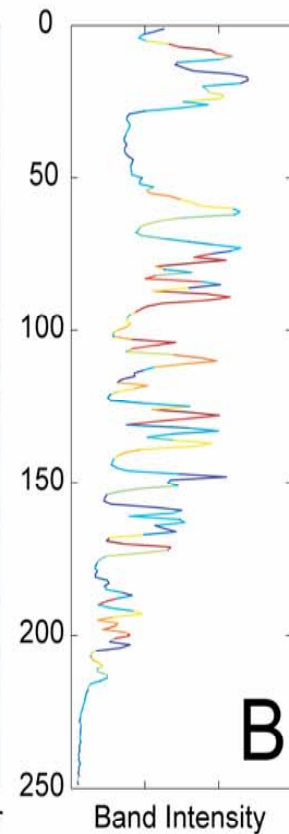
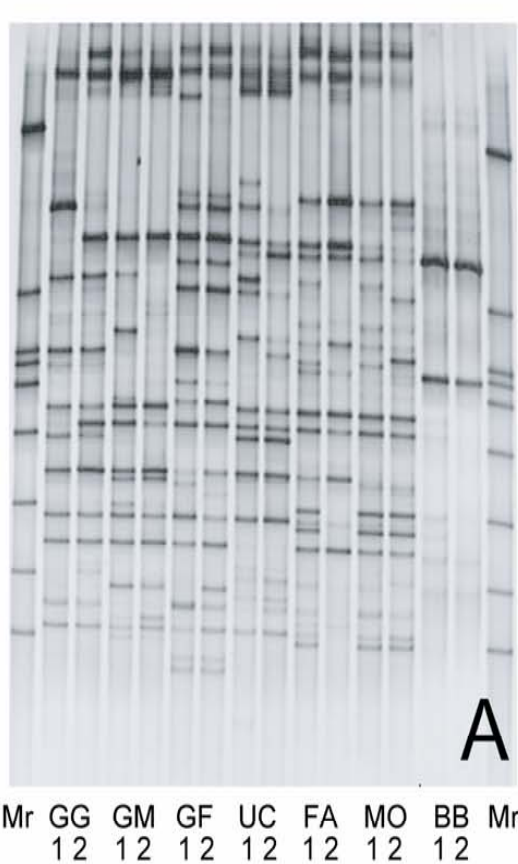


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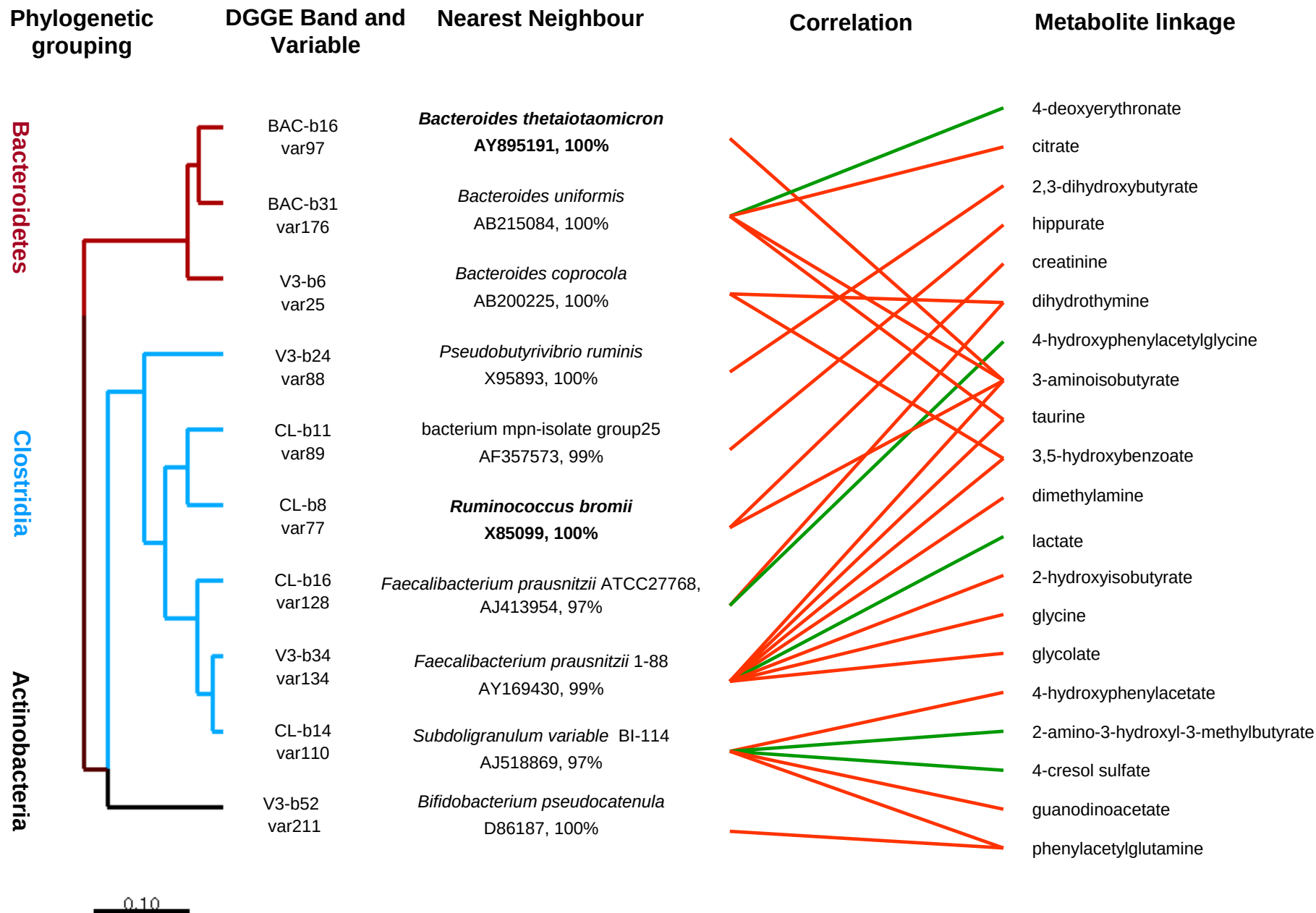


D





Q^2





http://www.upi.com/NewsTrack/Science/2008/02/06/study_maps_gut_microflora/6812/

Study maps gut microflora

Published: Feb. 6, 2008 at 10:24 AM

LONDON, Feb. 6 (UPI) -- A British-Chinese study has mapped the bacteria living in seven members of a Chinese family to determine the role of gut microbes in bodily processes.

The researchers from Imperial College London and China's Jiao Tong University said the makeup of each person's gut microflora influences their health, with abnormalities in gut microbes linked to diseases such as diabetes and obesity.

However, the relationship between different species of bacteria and different processes has previously been defined only at a broad level, the scientists said, noting that prior to their study, only five people had had their gut microflora profiled in depth, with that data being published.

"Now we have developed a new way of exploring the connections between bugs and man we can hope to find a 'Rosetta Stone' to translate the functional properties of the bugs and so improve therapies to treat disorders of the gut and related conditions," said Imperial College London Professor Jeremy Nicholson, lead author of the study.

The research, led by Professor Liping Zhao of Jiao Tong University in Shanghai, appears in the Proceedings of the National Academy of Science.

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Research Highlight

Nature Reviews Microbiology 6, 256-257 (April 2008) | doi:10.1038/nrmicro1880

Symbiosis: Who does what in the microbiome?

Susan Jones

Recent studies have shown that the complement of gut bacteria varies among individuals, but specific data linking the bacteria present to their functions in human physiology have been lacking. In a recent report, Min Li and colleagues describe a multidisciplinary approach to link the functions of the trillions of microbial gut bacteria — the human microbiome — to host metabolic phenotypes. Importantly, they pinpoint specific microorganisms that have defined roles in human metabolism using a functional genomics approach.



A four-generation Chinese family volunteered for the study. Faeces and urine were sampled on two separate occasions and analysed by molecular and spectroscopic techniques. Then, multivariate data analysis was used to identify relationships between individual bacterial species and metabolites. Sequencing of a faecal clone library revealed that all

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in PNAS during March 2008 -- updated monthly

Most-read rankings are recalculated at the beginning of the month and are based on full-text and pdf views.

37. Min Li, Baohong Wang, Menghui Zhang, Mattias Rantalainen, Shengyue Wang, Haokui Zhou, Yan Zhang, Jian Shen, Xiaoyan Pang, Meiling Zhang, Hua Wei, Yu Chen, Haifeng Lu, Jian Zuo, Mingming Su, Yunping Qiu, Wei Jia, Chaoni Xiao, Leon M. Smith, Shengli Yang, Elaine Holmes, Huiru Tang, Guoping Zhao, Jeremy K. Nicholson, Lanjuan Li, Liping Zhao
Symbiotic gut microbes modulate human metabolic phenotypes
Proc. Natl. Acad. Sci. USA Feb 12, 2008; 105: 2117-2122.

(In "Microbiology") [\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

人源菌群微型猪模型可用于分子机理研究 Human-flora associated pig model for molecular mechanistic studies

ORIGINAL ARTICLE

Inter-species transplantation of gut microbiota from human to pigs

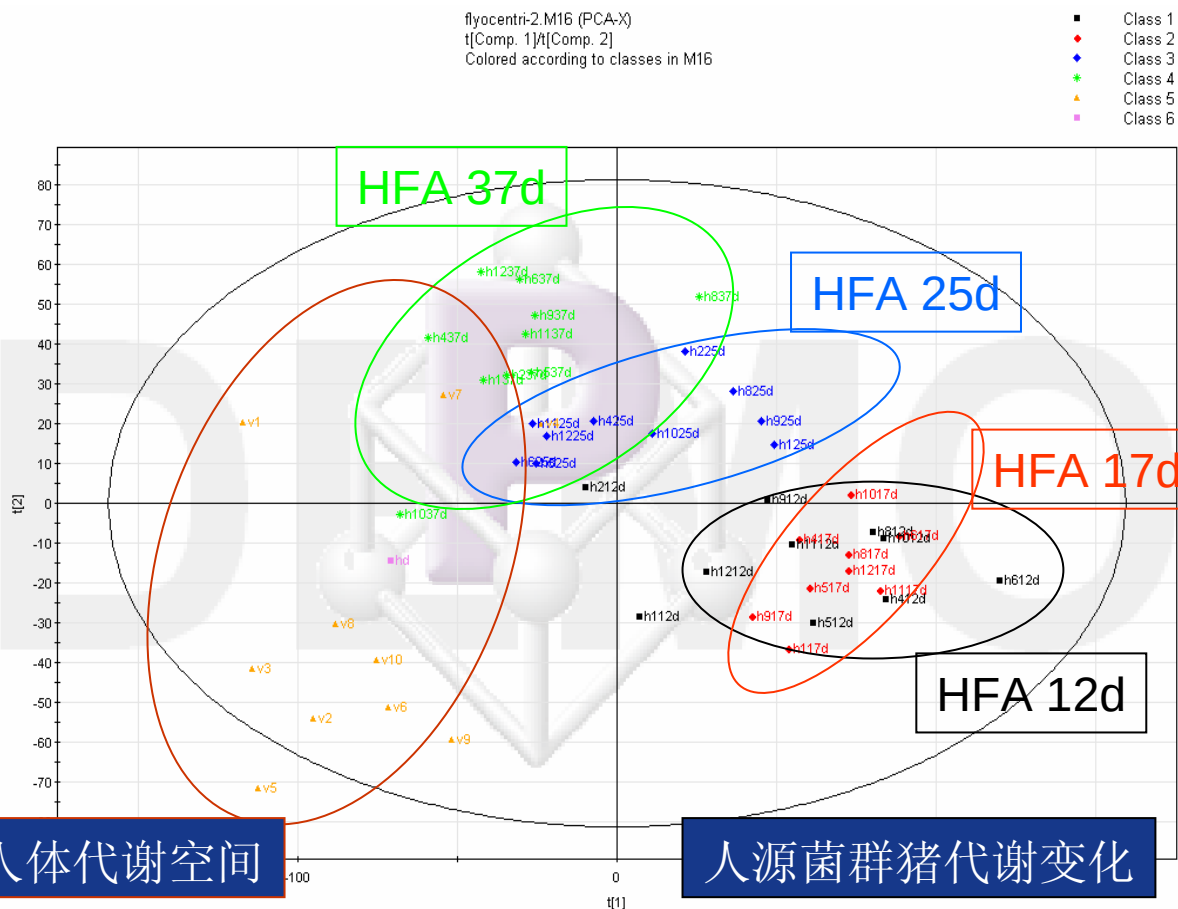
Xiaoyan Pang^{1,2}, Xiuguo Hua³, Qian Yang⁴,
Wei Jia⁶, Peter Bucheli⁷ and Liping Zhao²

¹Department of Bioscience and Biotechnology, College of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai, China; ²Key Laboratory of Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China; ³Key Laboratory of Animal Physiology and Biochemistry, Ministry of Agriculture, Nanjing, China; ⁴Tyco Clinic, Shanghai Jiao Tong University, Shanghai, China and



microbiota for unders
to its vast diversi
gut microbiota in
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nfree piglets was
y improved system
6–162; doi:10.1038
microbe and microt
g; gut microbiota; f

2003/04/29



R2X[1] = 0.400244
Ellipse: Hotelling T2 (0.95)

R2X[2] = 0.10411

赵立平组、华修国组



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Gut Microbiota and Diet-induced Metabolic Syndrome

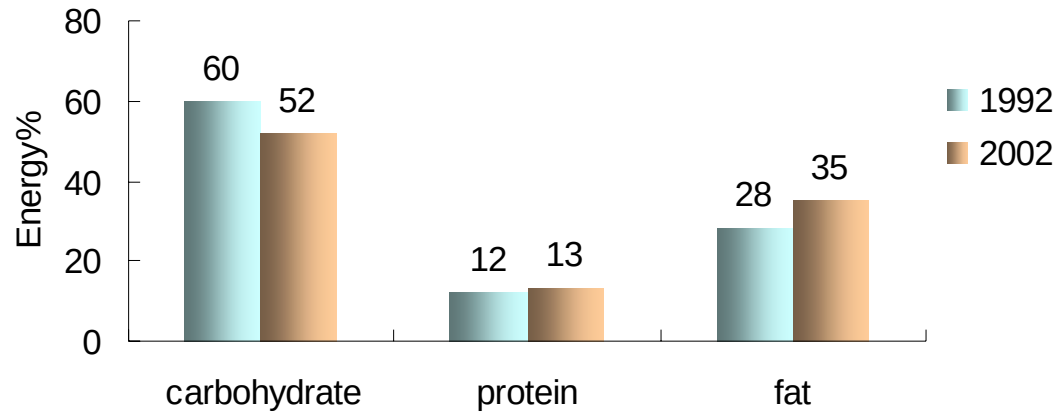
Liping Zhao
Shanghai Center for Systems Biomedicine
Shanghai Jiao Tong University



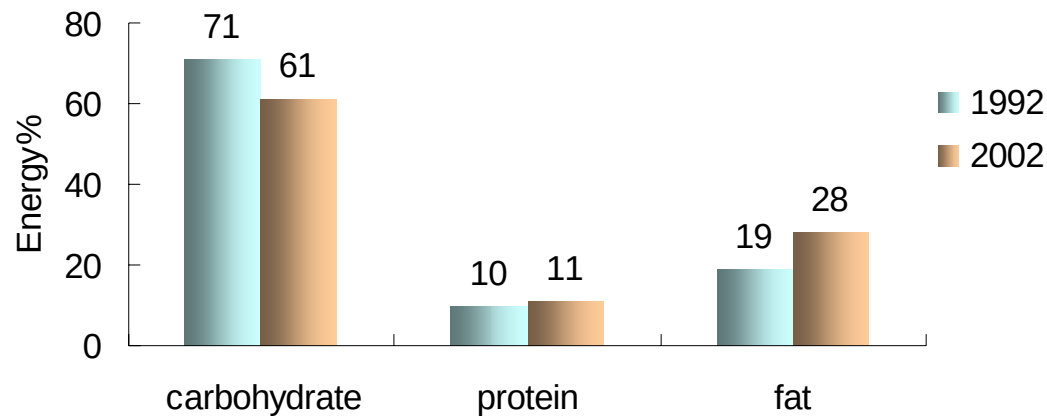
Nutritional Transition

Change of Energy Sources (1992 -2002)

Urban



Rural



Prevalence of Obesity

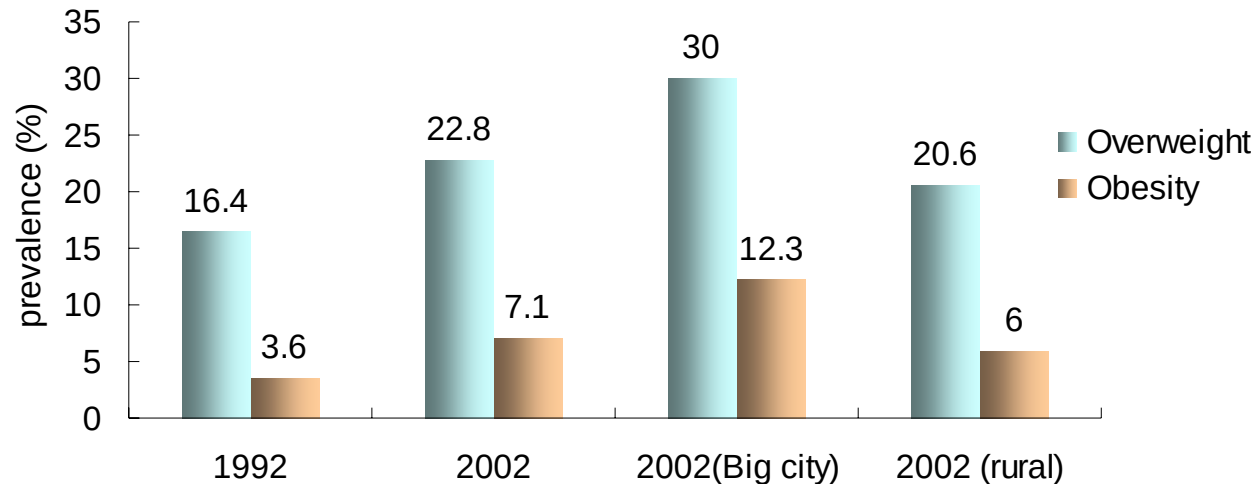
- **Worldwide** (WHO)

Overweight : 1,200,000,000

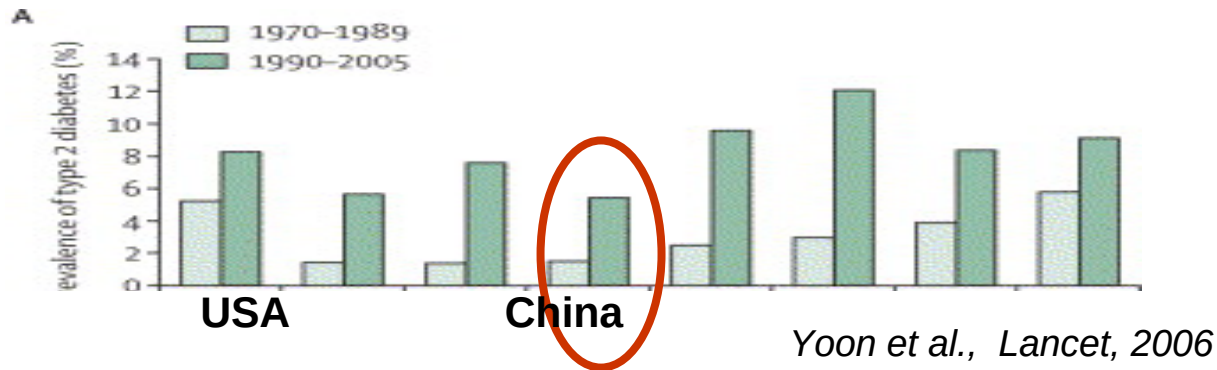
Obese: 300,000,000

- **China** (National Nutrition Survey, 2002)

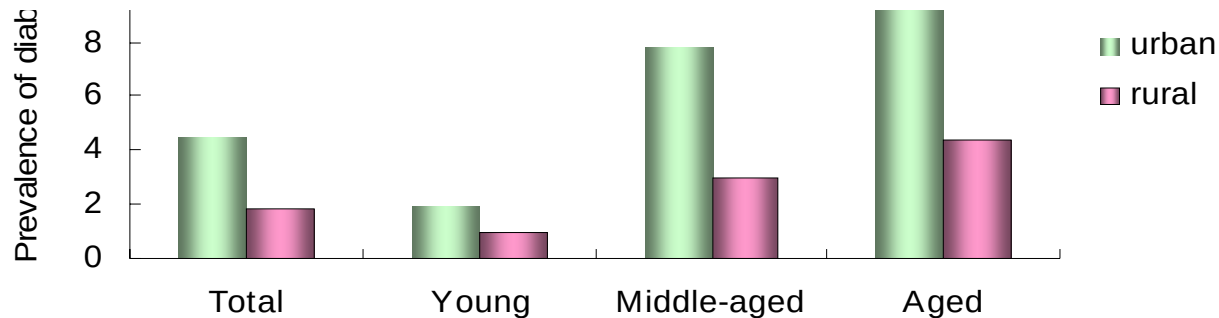
Chinese Adults (≥ 18 yrs)



Prevalence of Type 2 Diabetes



Prevalence of Type 2 Diabetes in Different Countries



Prevalence of Type 2 Diabetes in Chinese (≥ 18 yrs)

China National Nutrition Survey, 2002

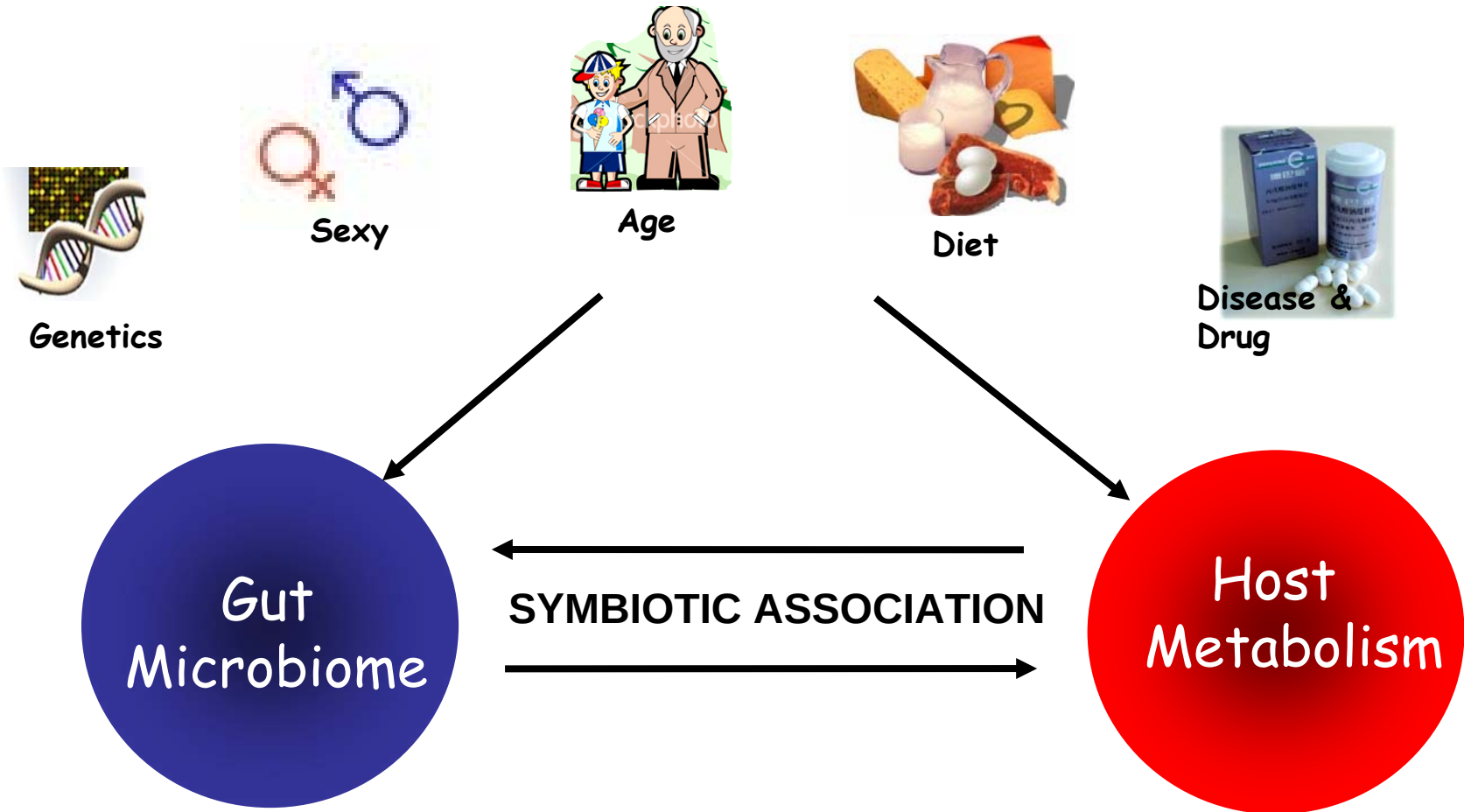


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环境、菌群、遗传与健康的关系

Environments, gut microbiota, genetics and health





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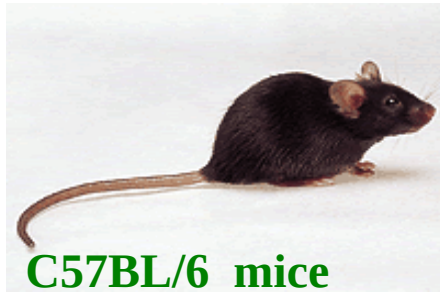
Interactions between gut microbiota, diet and host genotype for host health 食物、基因型和菌群互作影响宿主的健康

赵立平组、陈雁组
ZHAO Lab, CHEN Lab

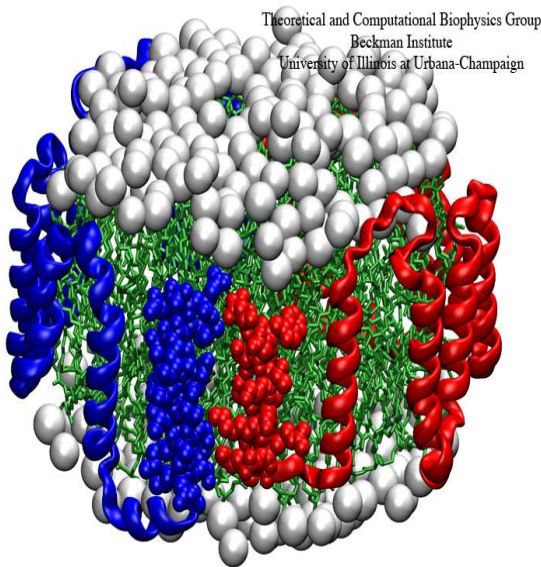
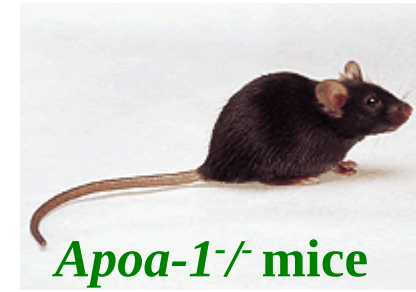


*Apoa-1*gene Knockout Mice

*Apoa-1*基因敲除小鼠



*Apoa-1*gene
→
knockout



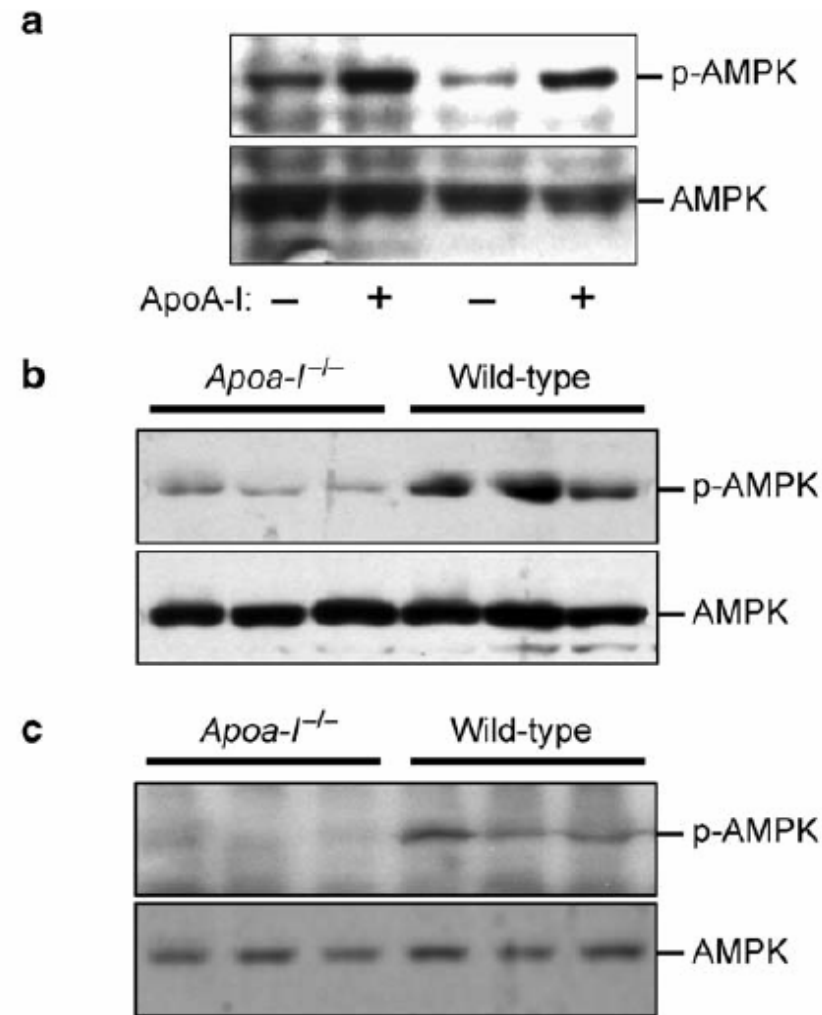
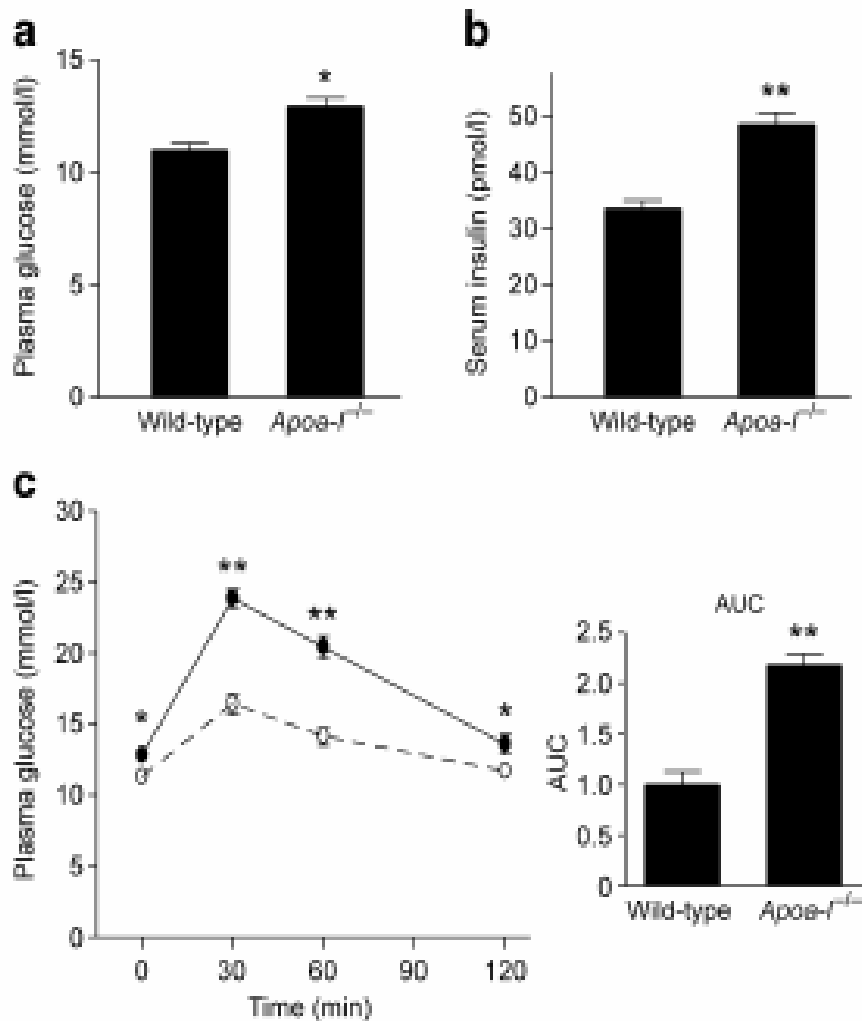
Apolipoprotein A- I

- Reduced HDL-cholesterol levels
- Susceptibility to high-fat dietary-induced atherosclerosis
- Insulin resistance and early symptoms of diabetes

Strategy for targeting the mouse *Apoa-1* gene.
(Williamson, 1992, PNAS)

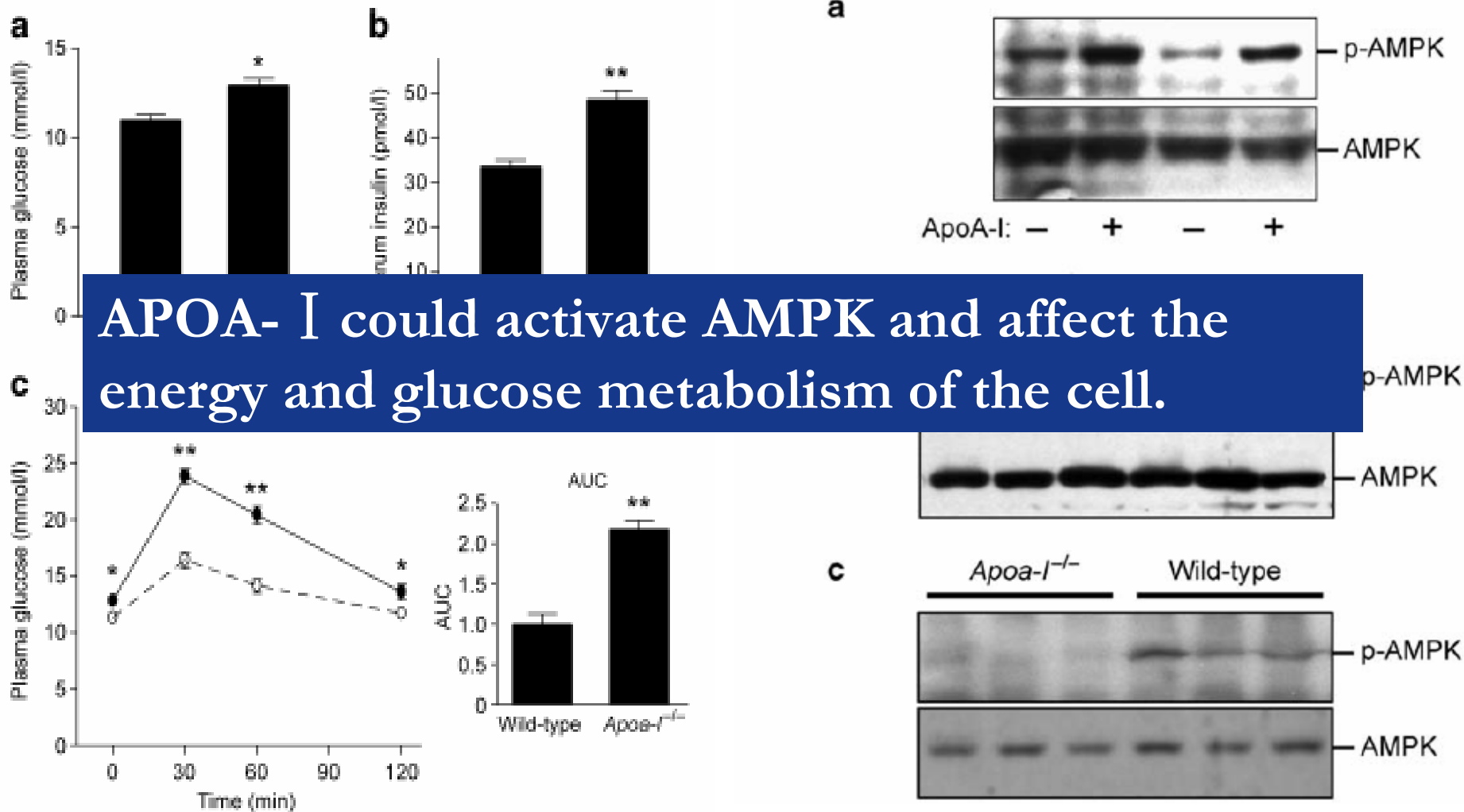


Apolipoprotein A- I and 2 type Diabetes



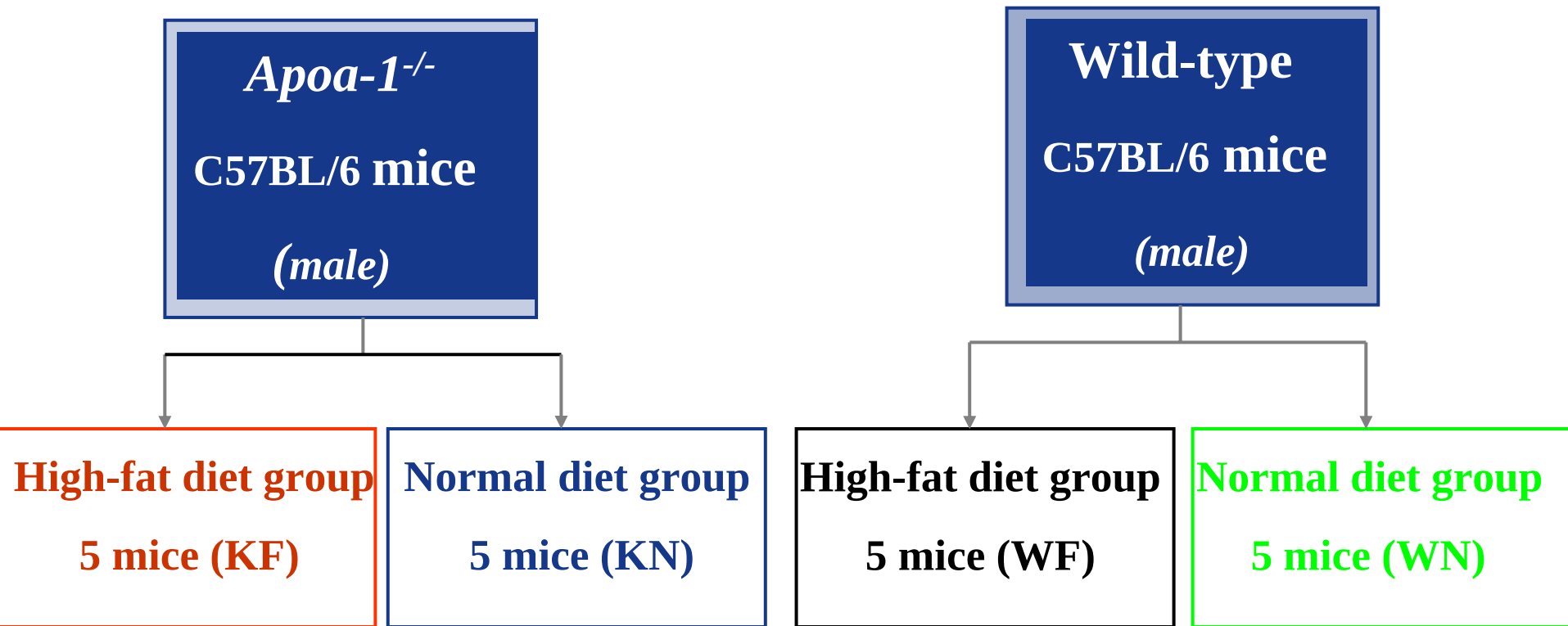


Apolipoprotein A- I and 2 type Diabetes



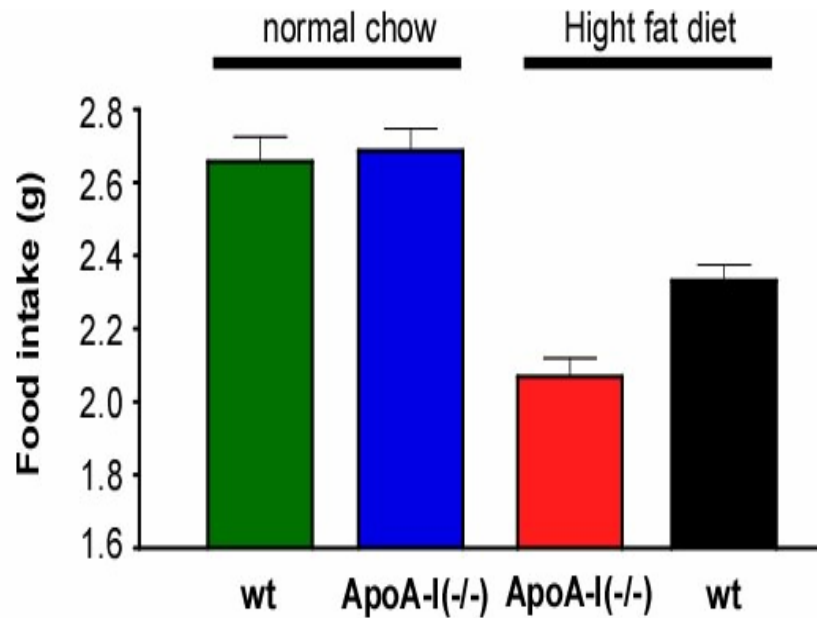


Animal trial scheme

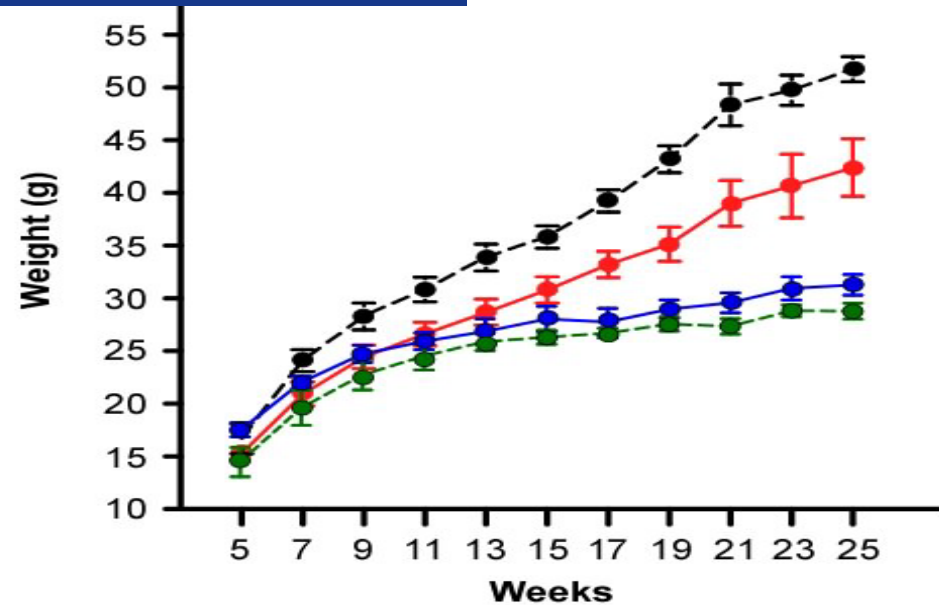




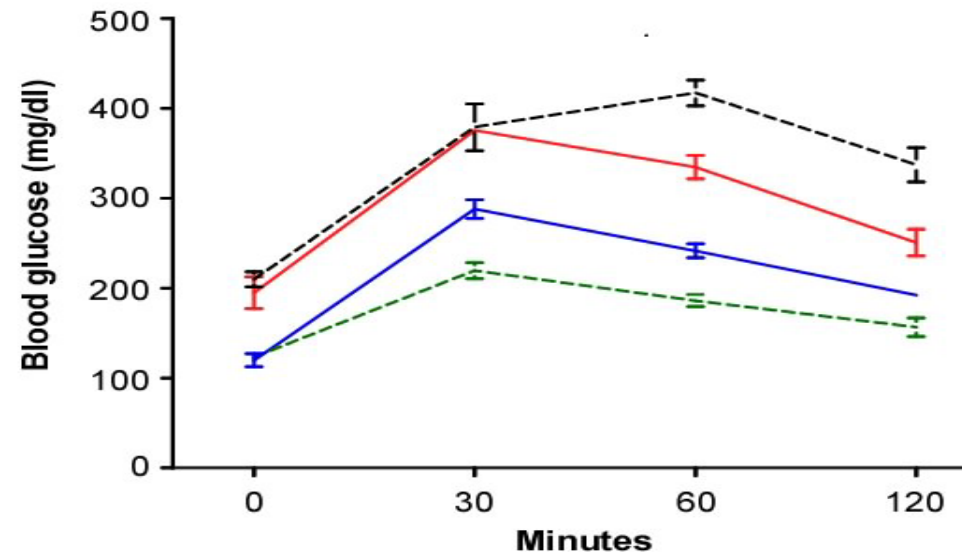
Food intake



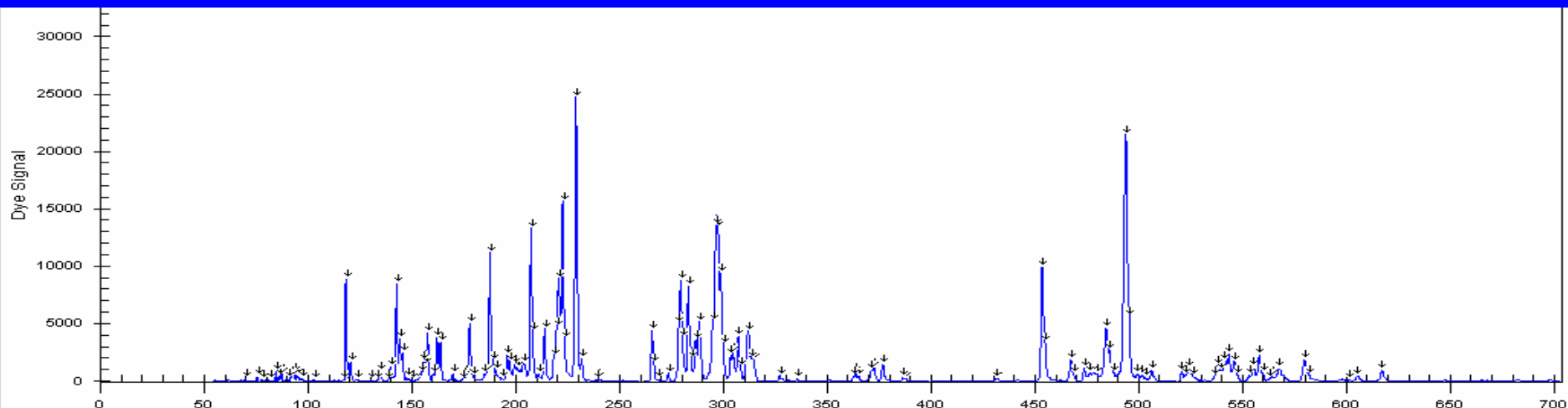
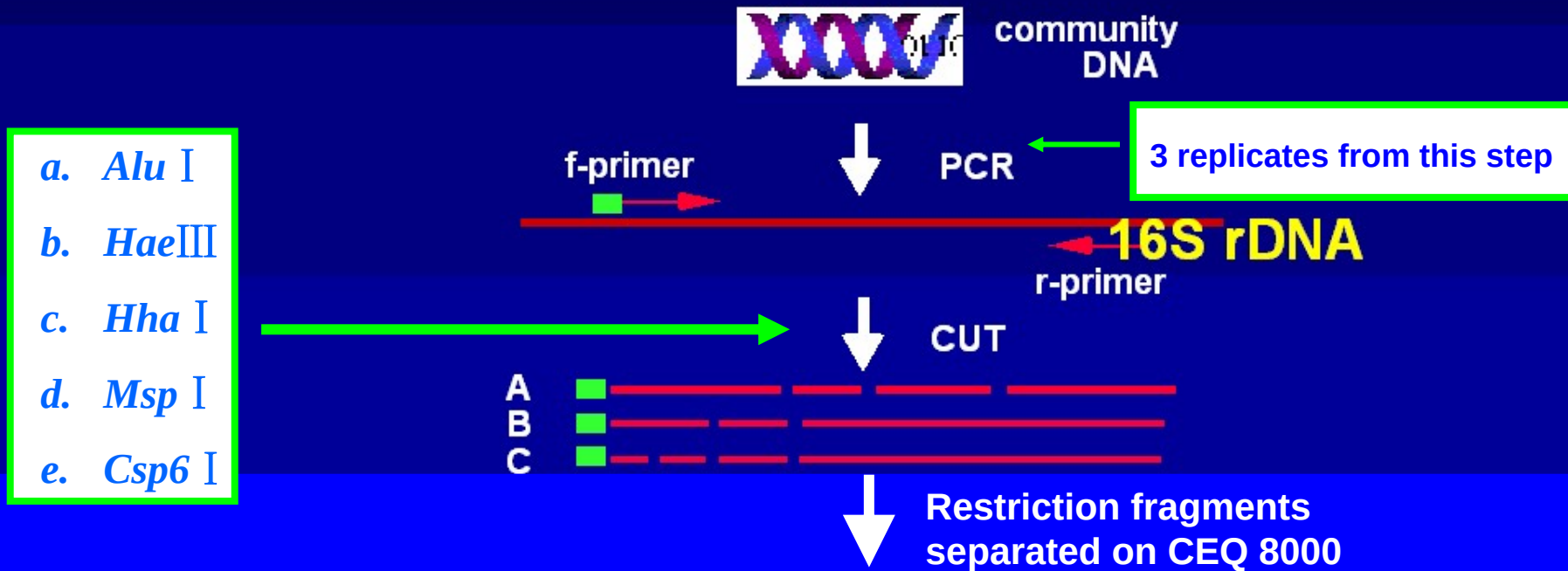
Growth Curve



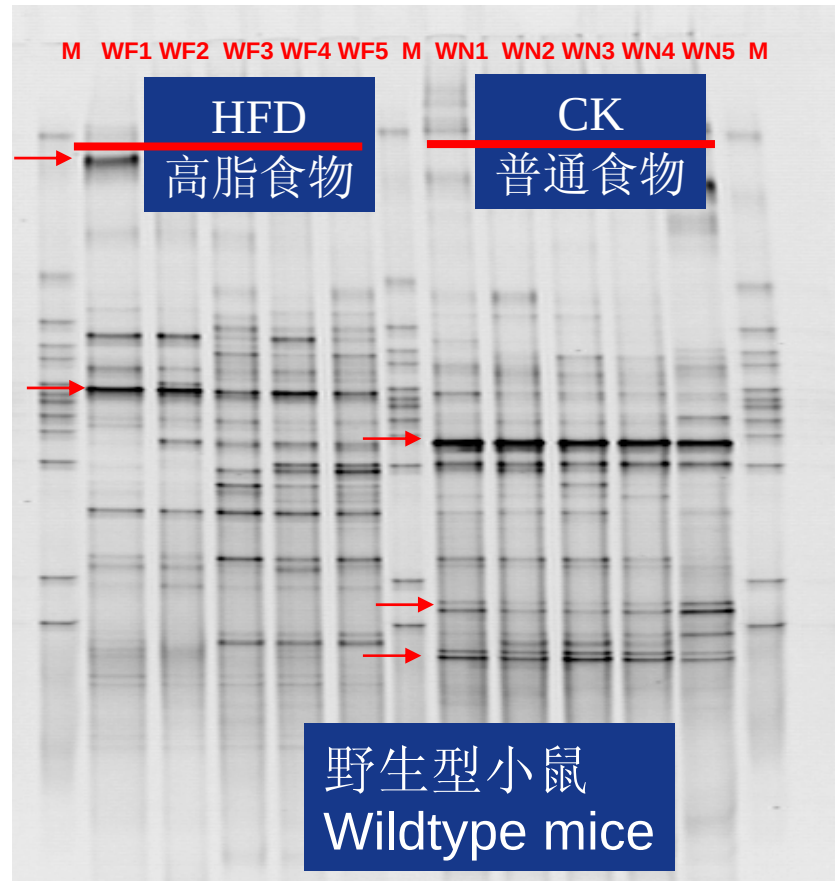
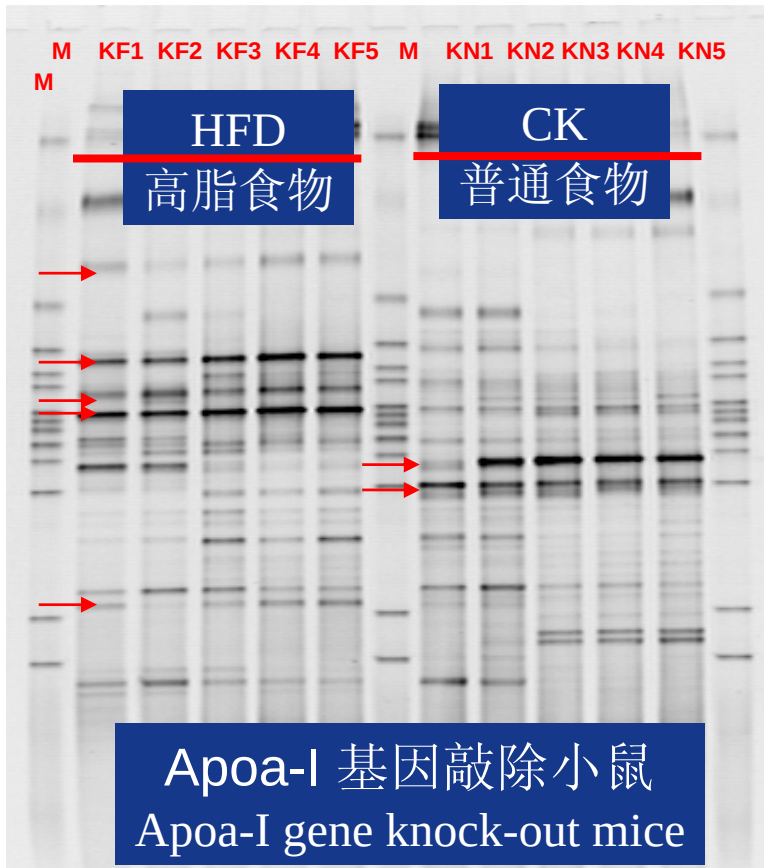
Glucose Tolerance Test



Terminal Restriction Fragment Length Polymorphism (T-RFLP)

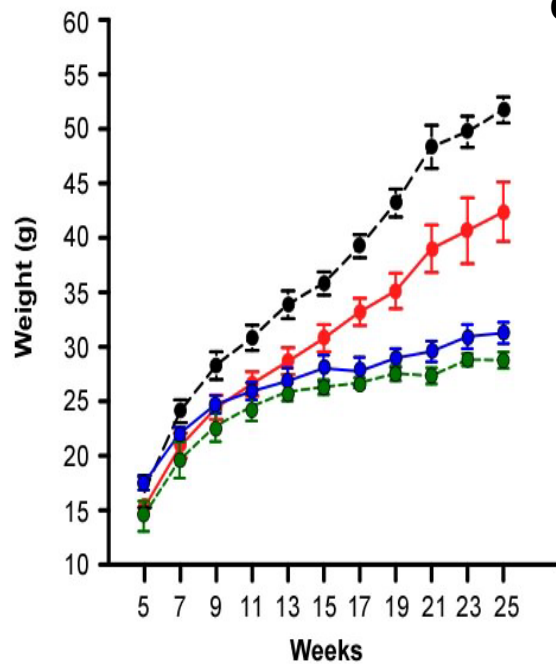


PCR-DGGE Fingerprinting



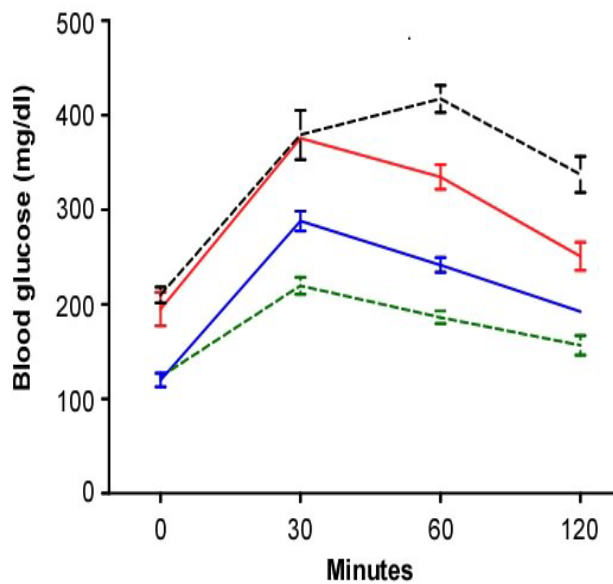
肠道菌群结构可以反映高脂食物和宿主基因型作用下的健康特征
Gut microbiota structure reflecting host health status

A
Growth Curve

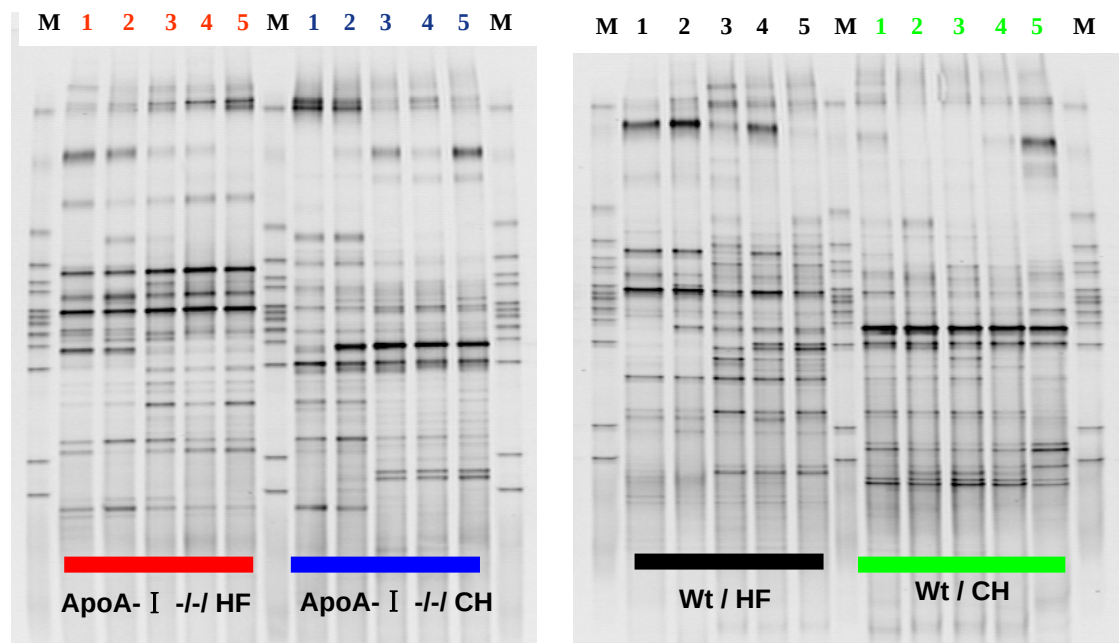


B

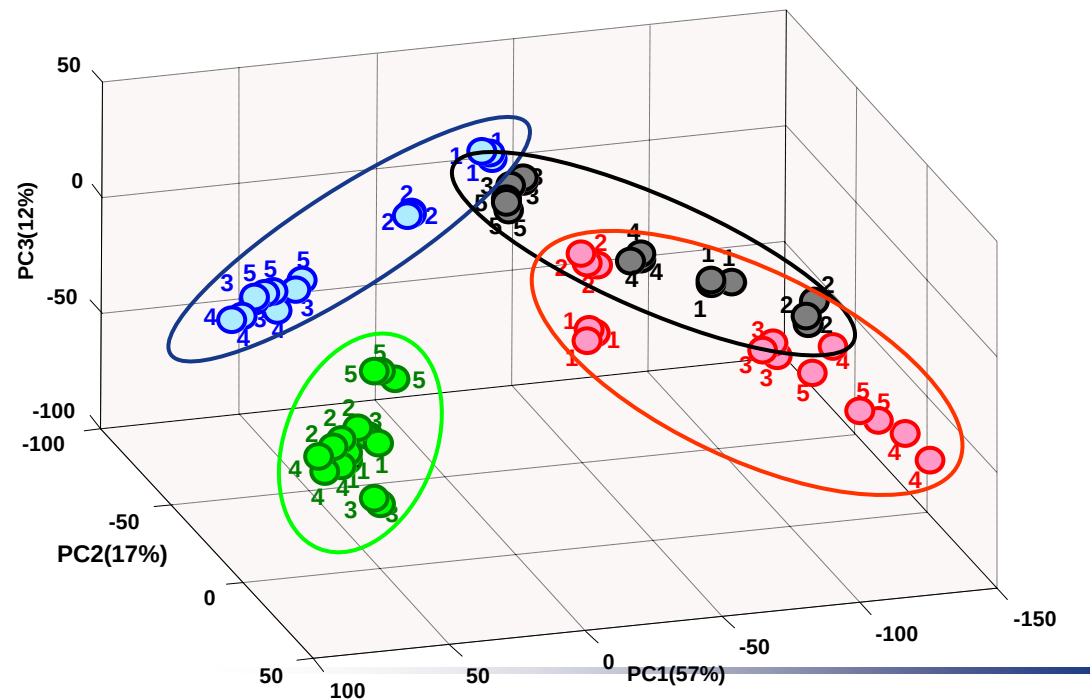
Glucose Tolerance Test



C

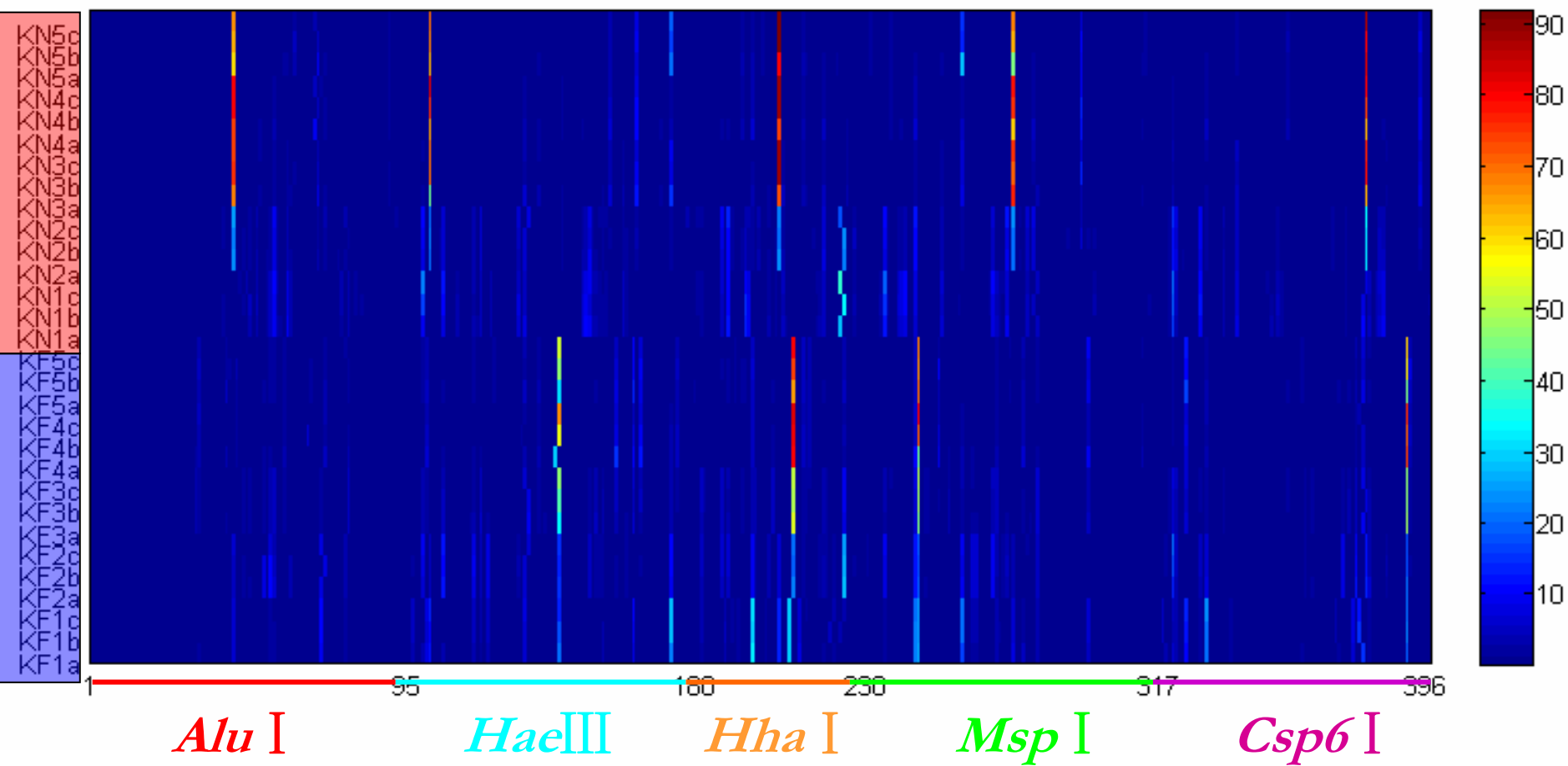


D

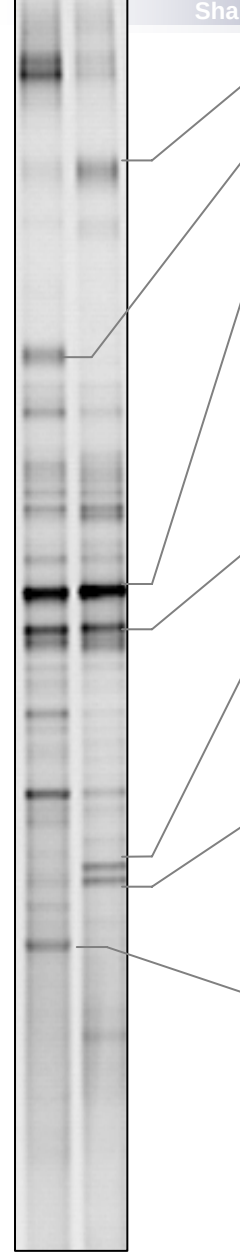




TRFs of KF and KN groups

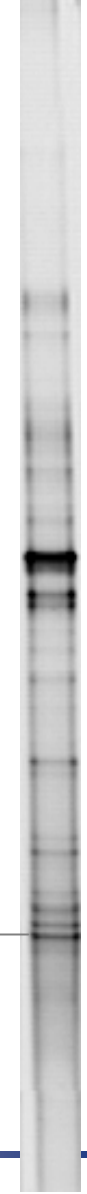


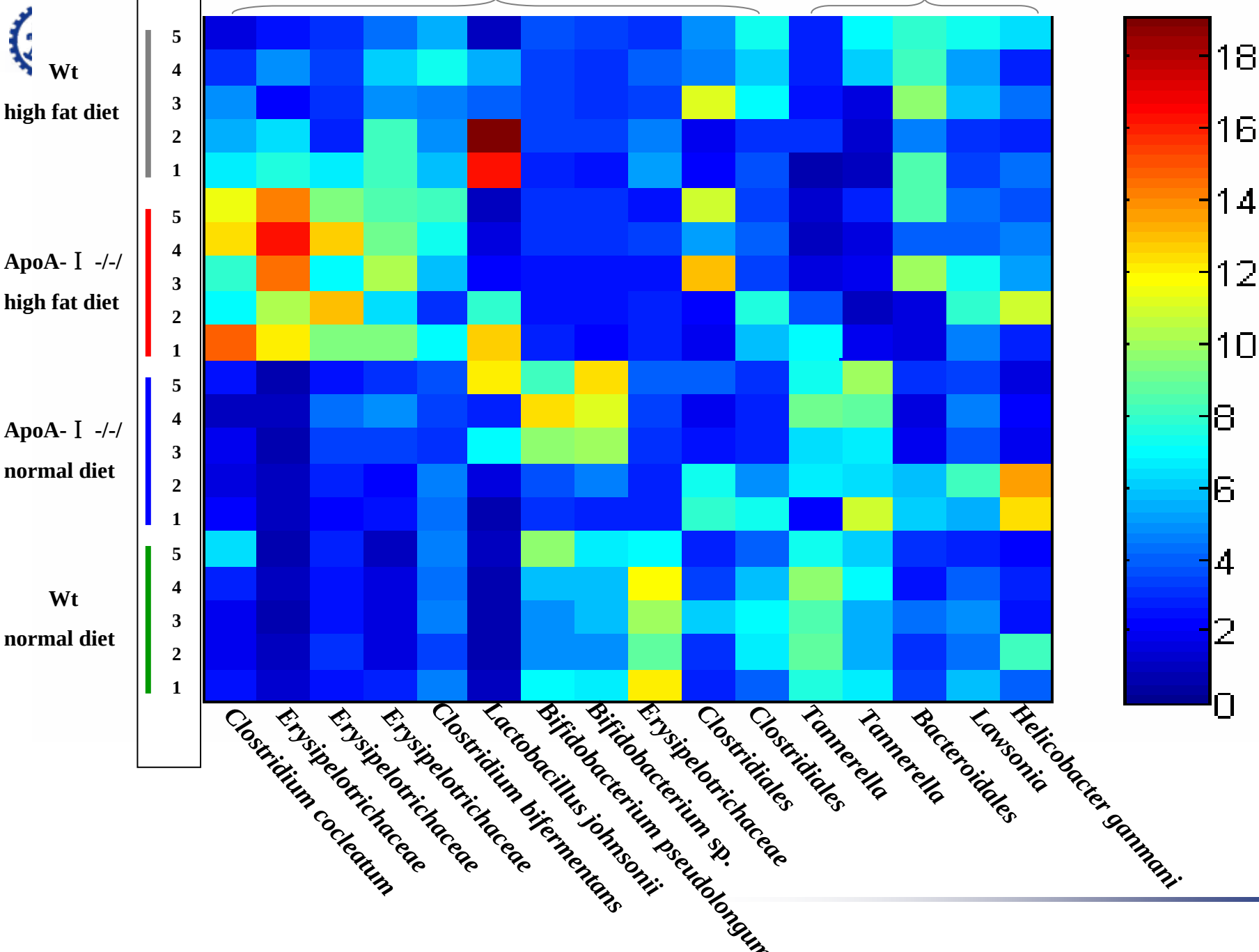
Normal chow /
Apoa- I^{-/-} /
NO.2 NO.3



Information of Closed Relatives			
Band	Similarity	Organism (Acession no.)	Phylogenetic affiliation
Shanghai Jiao Tong University			
8	100	<i>Lactobacillus johnsonii</i> (AB186343)	<i>Firmicutes, Bacilli, Lactobacillales, Lactobacillaceae, Lactobacillus</i>
15	100	<i>Helicobacter ganmani</i> (T) (AF000221)	<i>Proteobacteria, Epsilonproteobacteria, Campylobacterales, Helicobacteraceae, Helicobacter</i>
6	98	uncultured bacterium (DQ815337)	<i>Bacteroidetes, Bacteroidetes, Bacteroidales, Porphyromonadaceae, Tannerella</i>
	80	<i>Porphyromonas gulae</i> (ATCC51700)	<i>Bacteroidetes, Bacteroidetes, Bacteroidales, Porphyromonadaceae, Porphyromonas</i>
7	99	uncultured bacterium (DQ815337)	<i>Bacteroidetes, Bacteroidetes, Bacteroidales, Porphyromonadaceae, Tannerella</i>
	81	<i>Porphyromonas circumdentaria</i>	<i>Bacteroidetes, Bacteroidetes, Bacteroidales, Porphyromonadaceae, Porphyromonas</i>
10	100	<i>Bifidobacterium pseudolongum</i> subsp. <i>Pseudolongum</i> (AB186304)	<i>Actinobacteria, Actinobacteridae, Bifidobacteriales, Bifidobacteriaceae, Bifidobacterium</i>
11	100	uncultured bacterium (EU511073)	
	98	<i>Bifidobacterium animalis</i> subsp. <i>Animalis</i> (AB186294)	<i>Actinobacteria, Actinobacteridae, Bifidobacteriales, Bifidobacteriaceae, Bifidobacterium</i>
16	99	uncultured bacterium (EF098678)	<i>Firmicutes</i>
	93	<i>Bryantella formatexigens</i> (T) (AJ318527)	<i>Firmicutes, Clostridia, Clostridiales, Clostridiaceae, Bryantella</i>
12	99	uncultured bacterium (EF099100)	<i>Firmicutes, Mollicutes, Incertae sedis 8, Erysipelotrichaceae</i>
	86	<i>Eubacterium cylindroides</i> (L34617)	<i>Firmicutes, Clostridia, Clostridiales, Eubacteriaceae, Eubacterium</i>

Normal chow /
wt /
NO.2



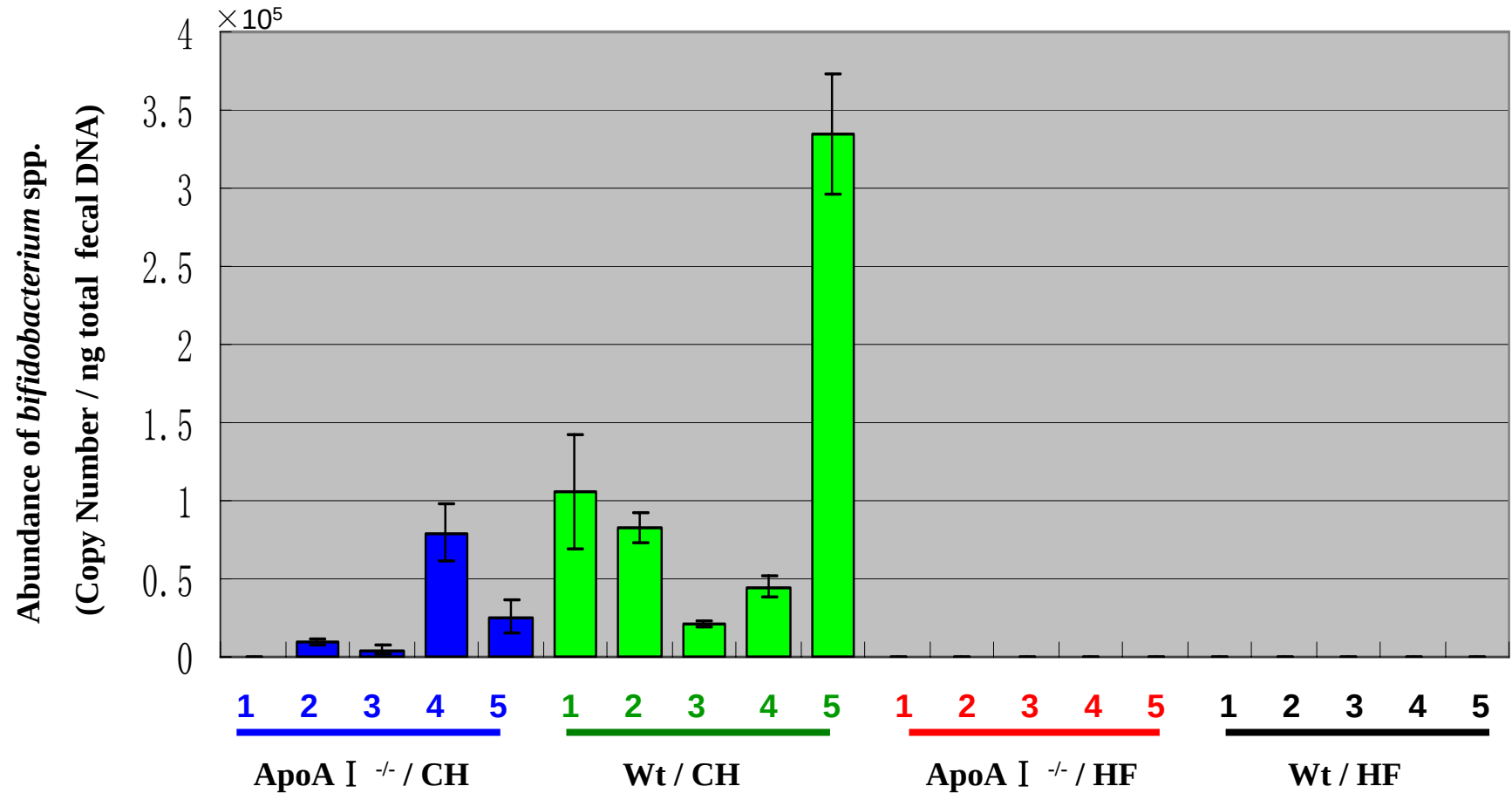




Band10 and Band 11 were *Bifidobacterium* spp.

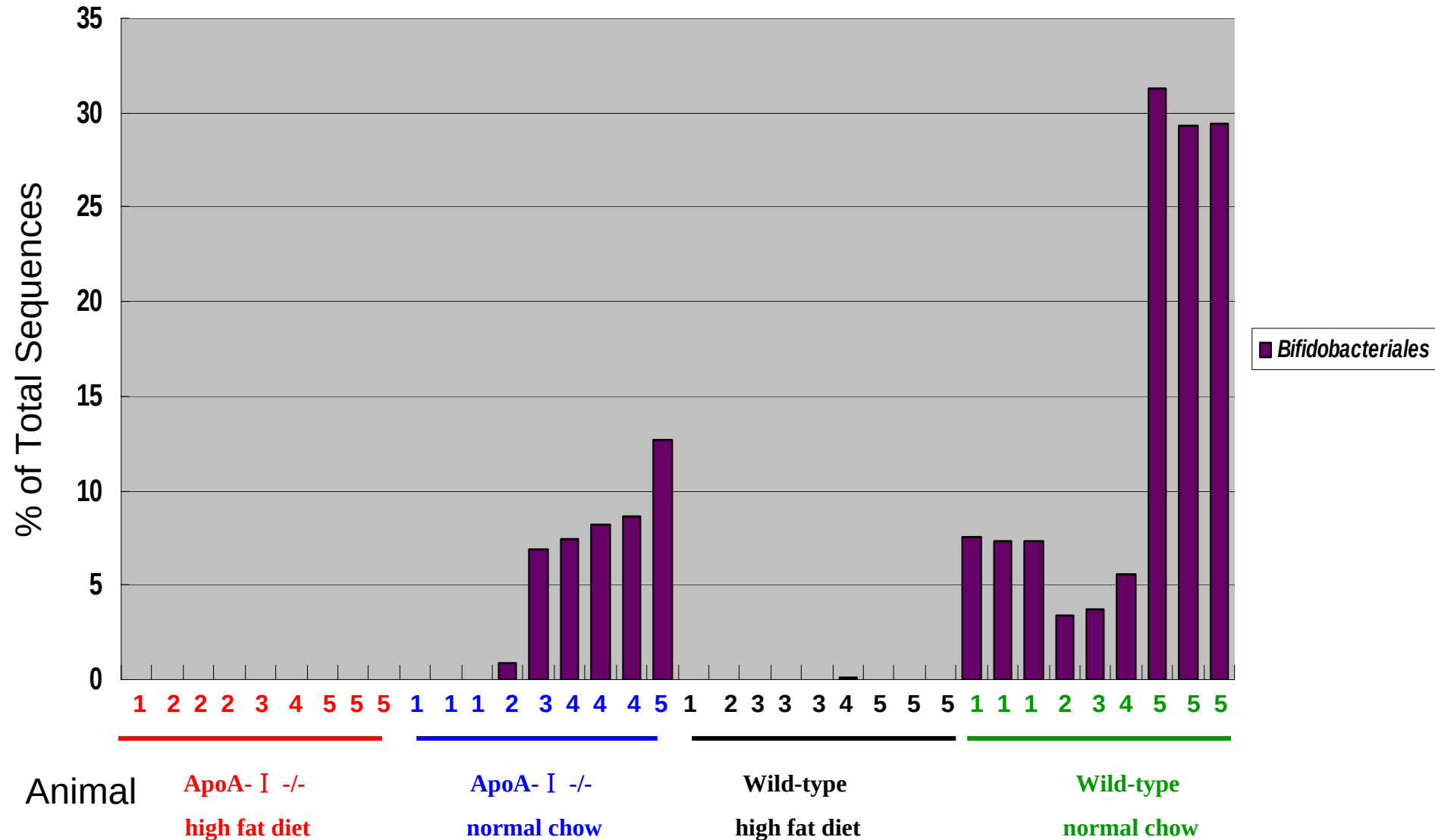


RT-PCR of *Bifidobacterium* spp.

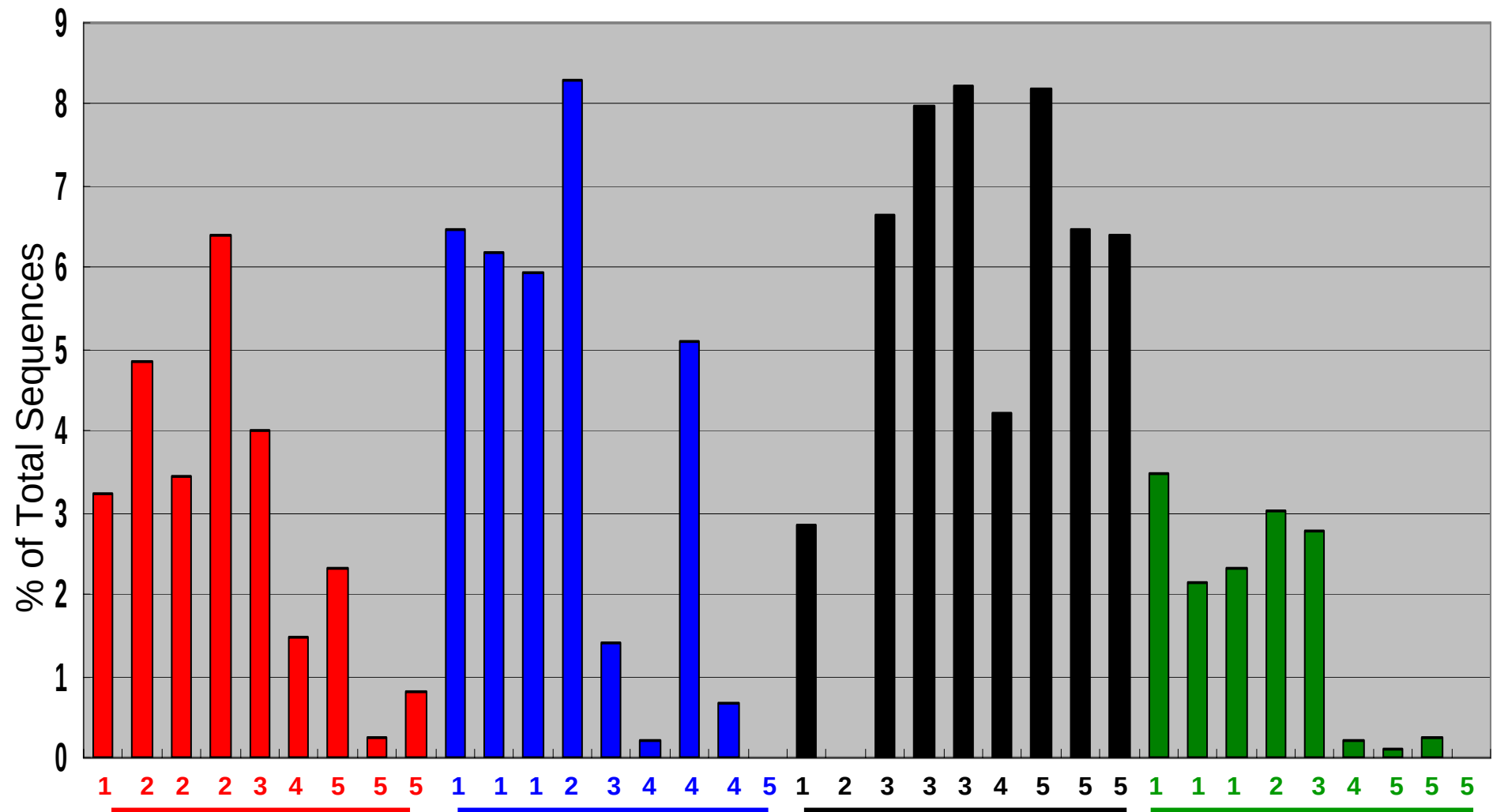




Abundance distribution of Bifidobacteria based on 454 sequencing



Proteobacteria



Animal

ApoA- I -/-
high fat diet

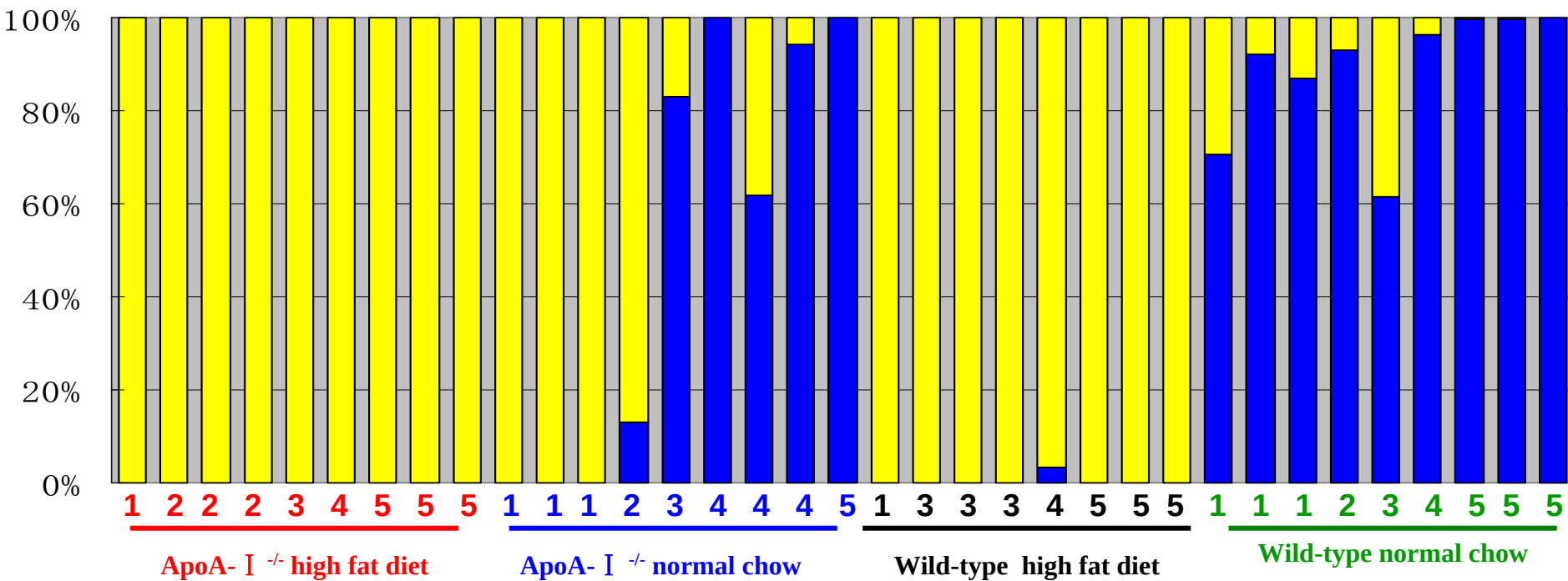
ApoA- I -/-
normal chow

Wild-type
high fat diet

Wild-type
normal chow



Bifidobacteriales vs. *Desulfovibrionales*



Bifidobacteriales -protecting gut barrier integrity
Desulfovibrionales -producing endotoxin (LPS)



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肠道菌群结构“分离分析”与 宿主健康动态监测

Structural segregation analysis of gut microbiota and host health monitoring

高脂食物、菌群变化与肥胖的发展
High fat diet, gut microbiota and obesity

ZHAO lab, JIA lab
赵立平组， 贾伟组

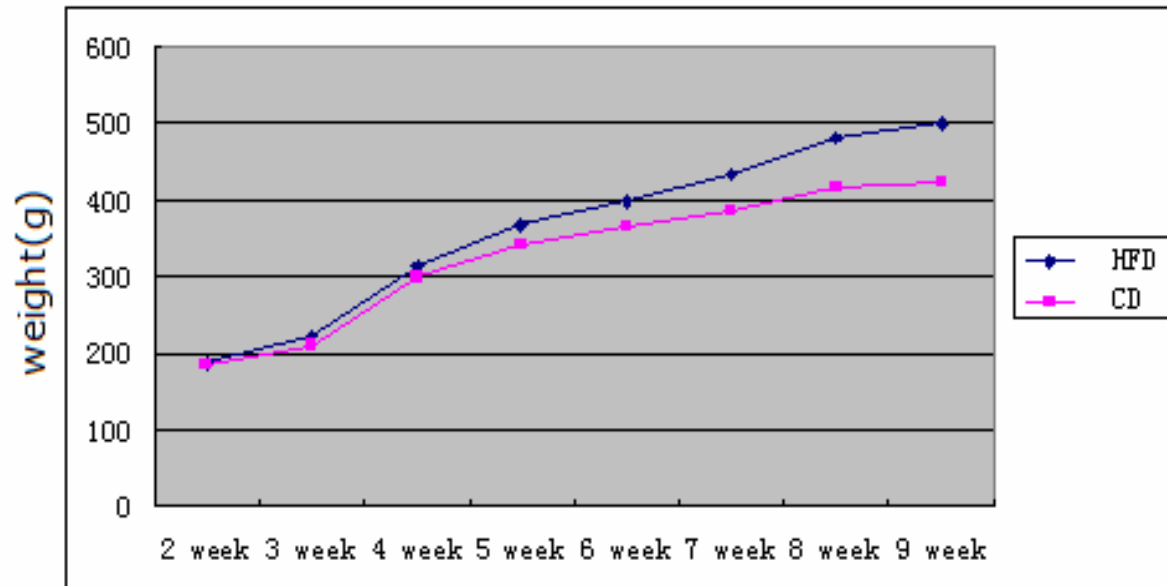


Progression of high fat diet induced obesity

高脂食物诱发的肥胖的发展

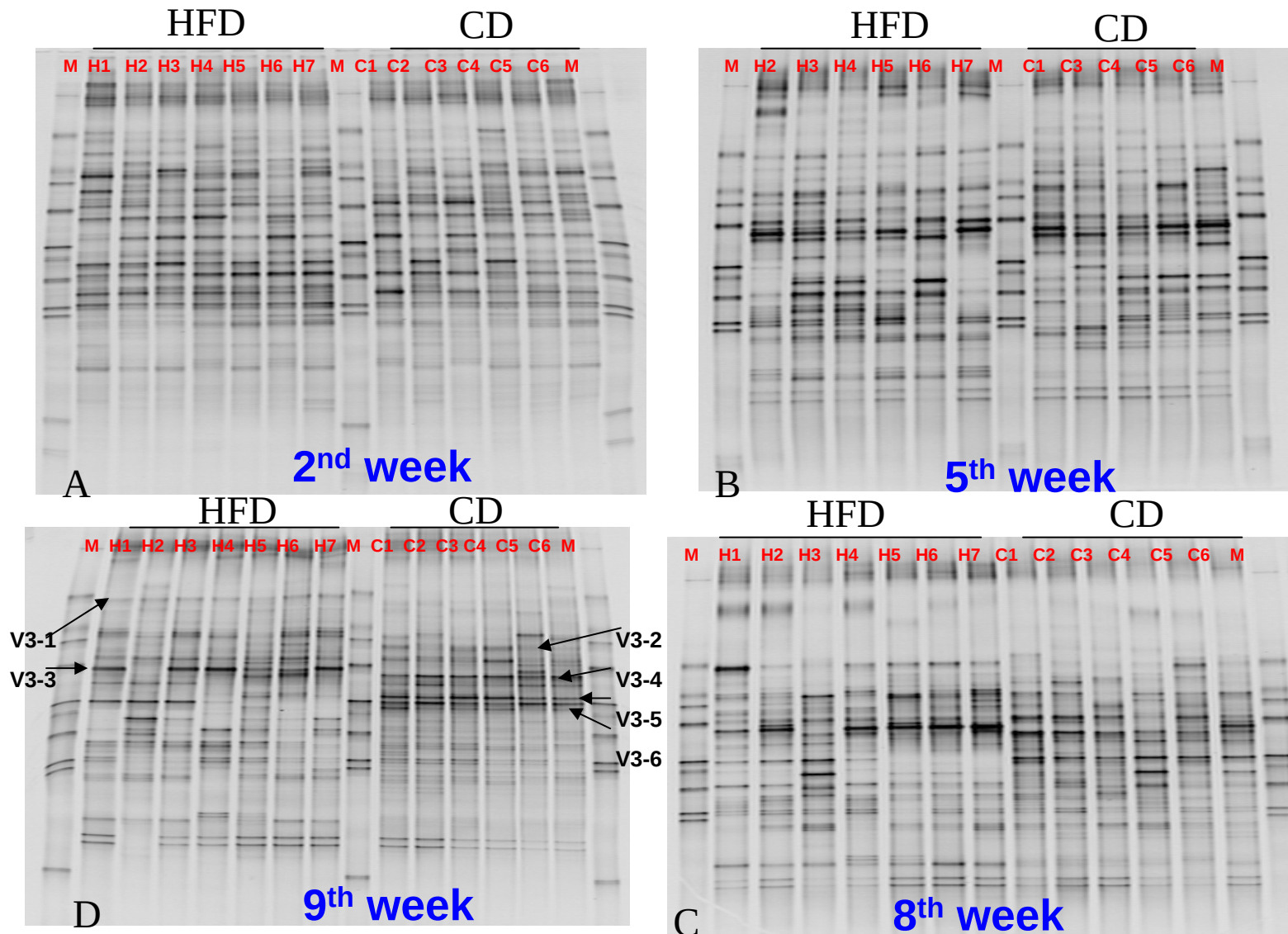
group \ week	2 nd week*	3 rd week*	4 th week*	5 th week*	6 th week*	7 th week**	8 th week***	9 th Week***
HFD	187±2	225±12	315±17	368±20	399±21	437±24	485±31	502±32
CD	185±3	212±7	299±21	344±30	365±38	386±41	416±47	424±48

*P>0.05



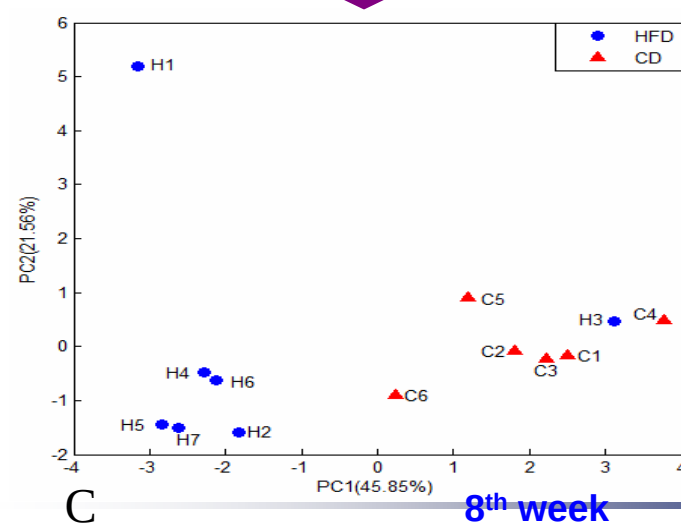
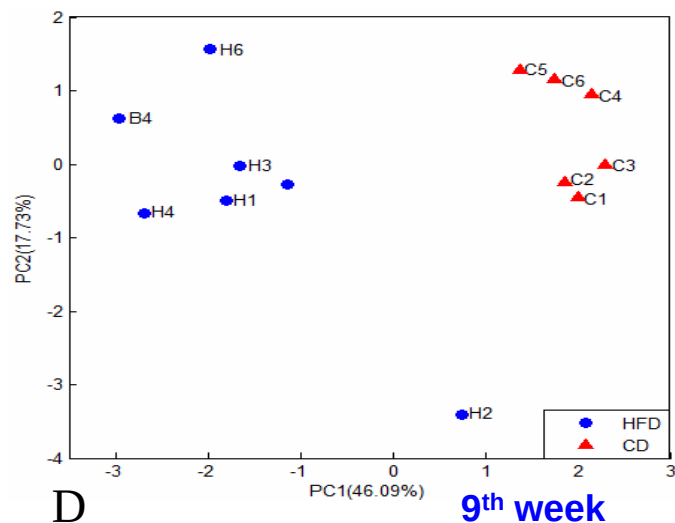
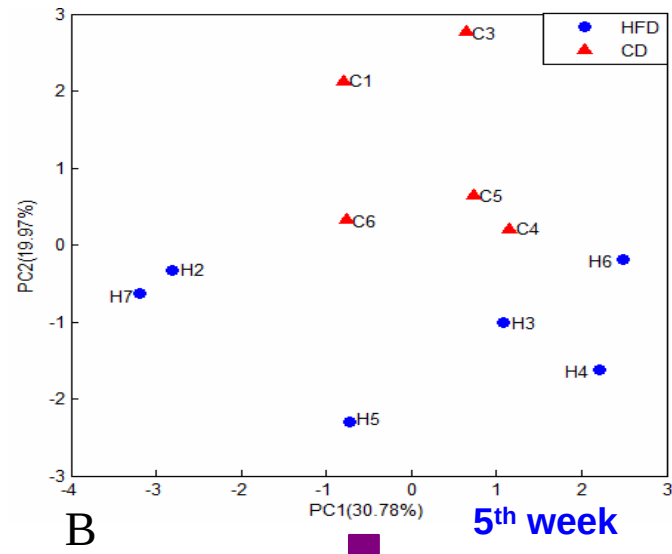
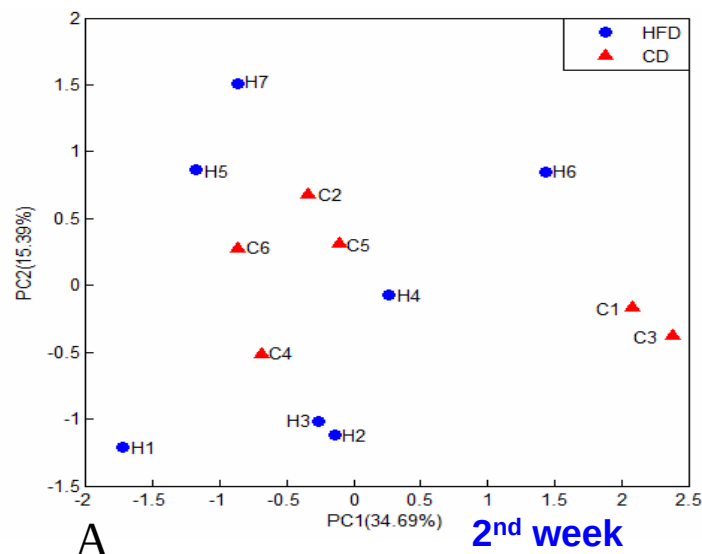
Structural segregation of gut microbiota during obesity progression

肠道菌群结构随肥胖发展而变化



Structural segregation of gut microbiota during obesity progression

肠道菌群结构随肥胖发展而变化

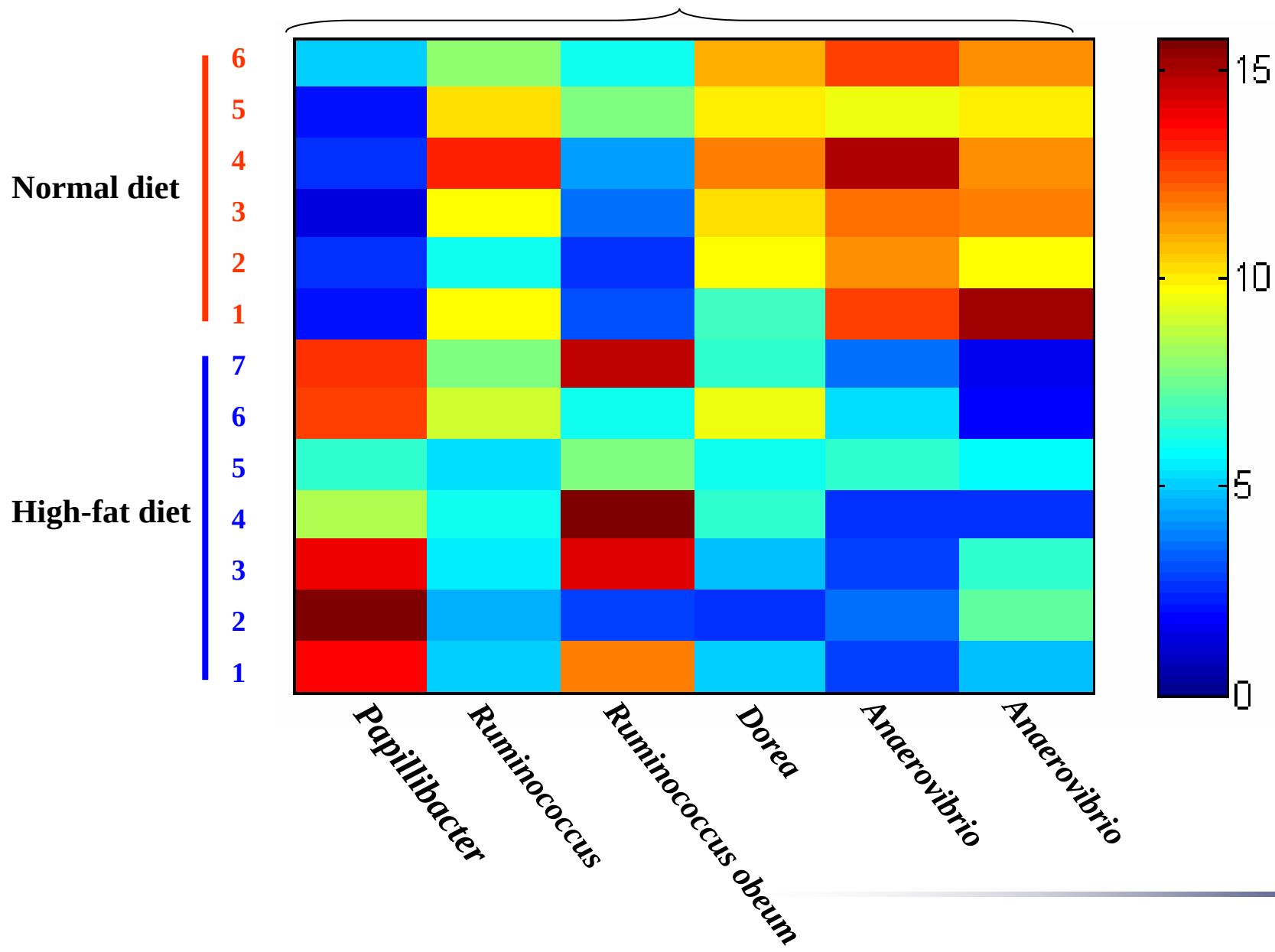




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Gram-positive





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Shanghai Jiao Tong University



Structural shifts of gut microbiota induced by carcinogen during precancerous lesion development

致癌剂诱导癌前病变过程中 肠道菌群结构的动态变化

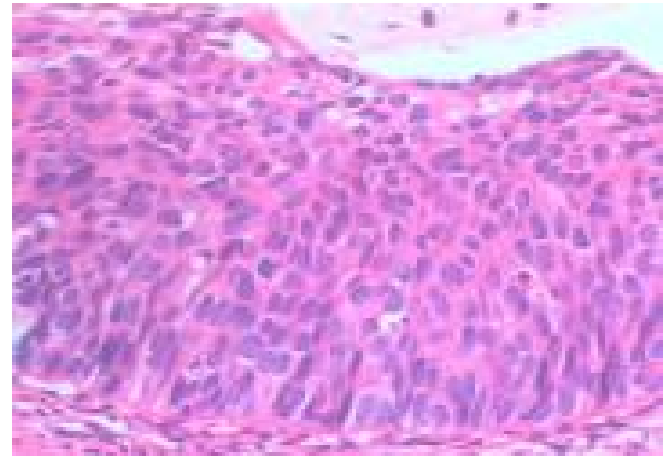
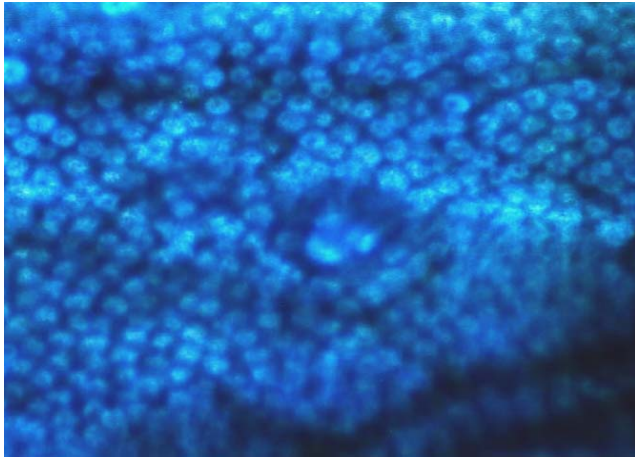




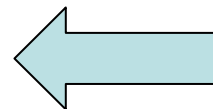
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Development of Colorectal cancer



Dysplasia



ACF under a light microscopy ($\times 40$)

adenocarcinoma

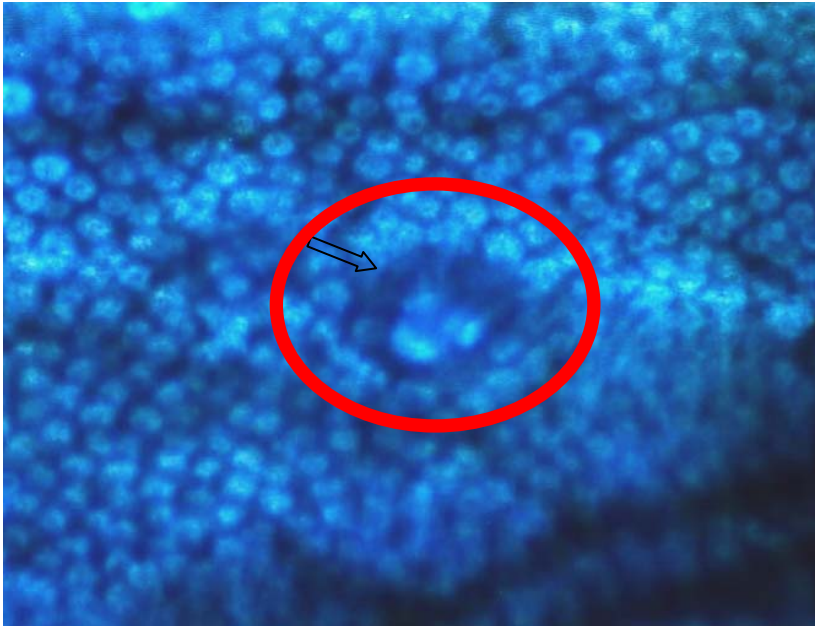
polypous adenoma



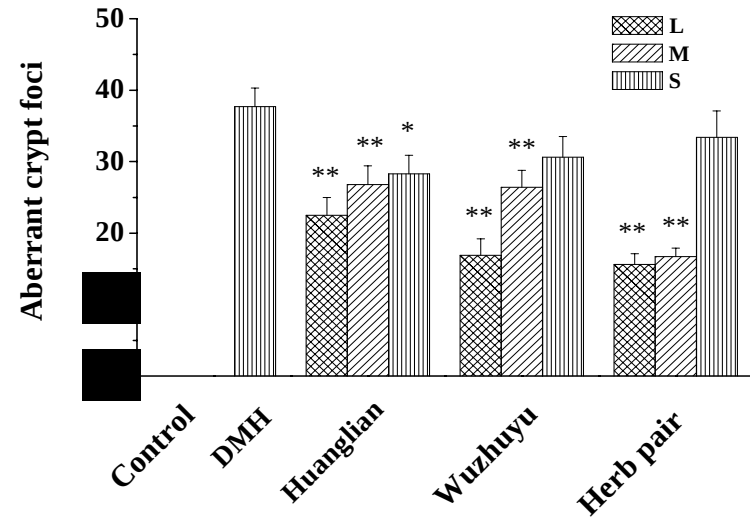
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Shanghai Jiao Tong University

结肠癌的癌前病变模型 Precancerous lesion of colon cancer



Aberrant crypt foci (ACF) induced by 1,2-dimethylhydrazine (DMH)

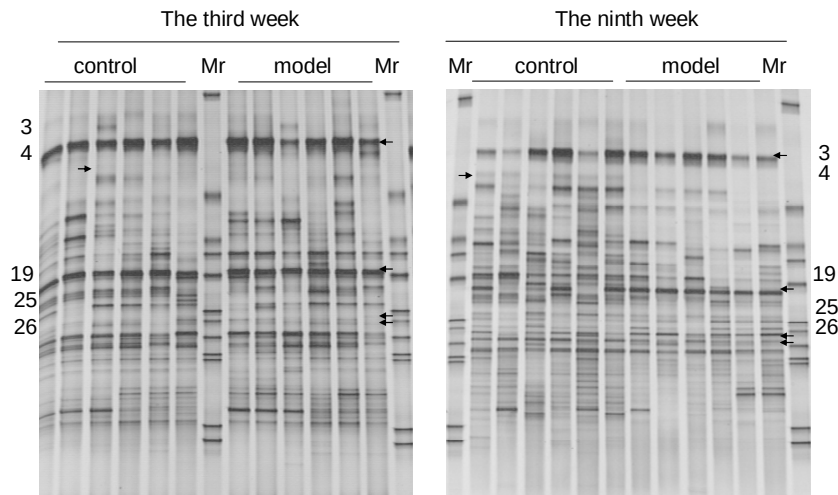


Reduction of ACF formation by TCM herbal extracts

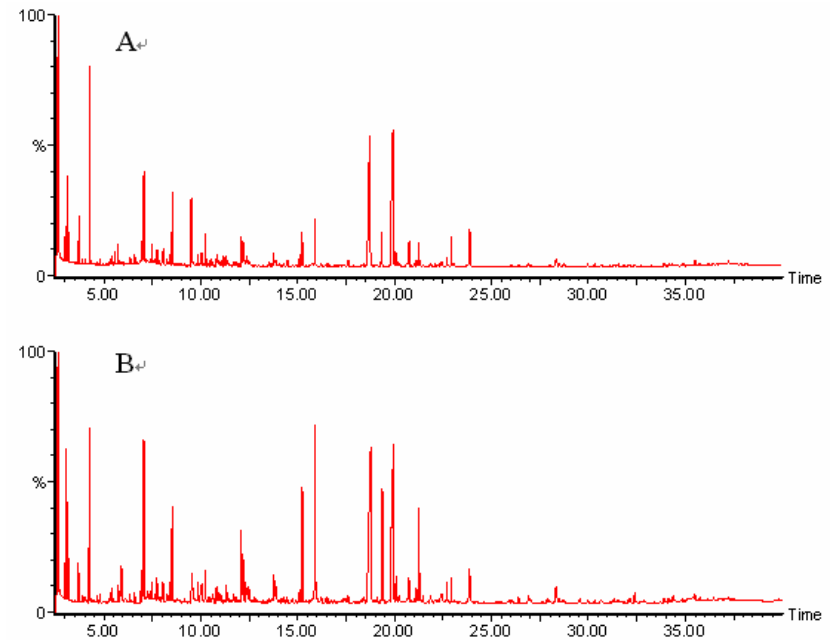
Wu group, Jia group, Zhao group

肠道菌群与宿主代谢的监测

Monitoring of host metabolism and gut microbiota



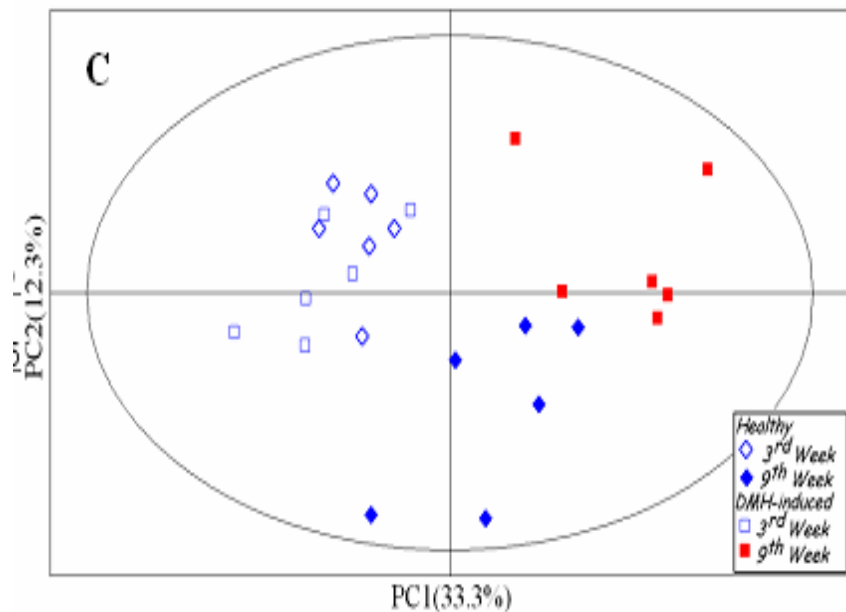
DNA fingerprinting of gut microbiota



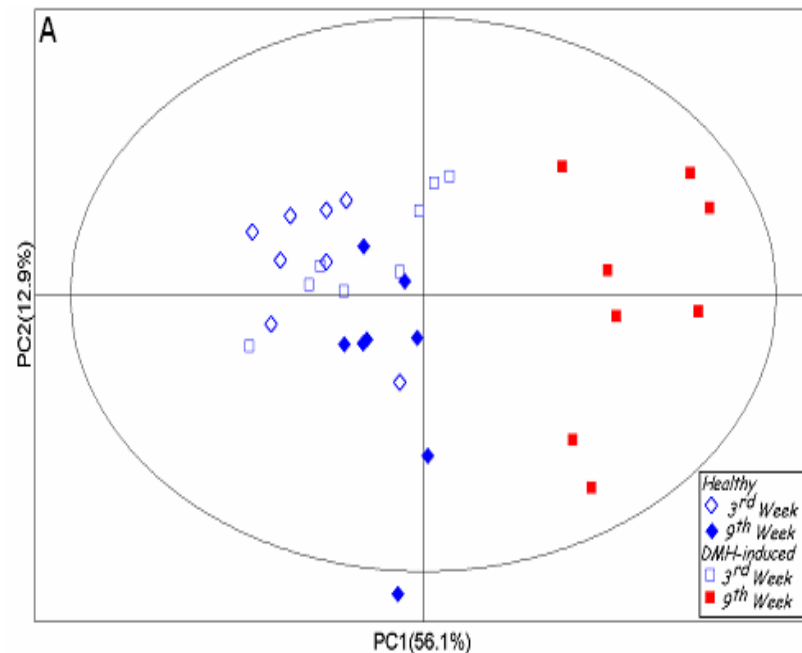
GC/MS profiling of host metabolism



癌前病变动物菌群结构和整体代谢特征的变化



菌群结构变化
Gut microbiota structure



整体代谢变化
Global metabolism

Concomitant shifts of gut microbiota and host global metabolism
away from healthy control during precancerous lesion formation in DMH treated group

区别癌前病变动物和健康动物的关键代谢物

Key metabolites for differentiation between healthy and precancerous animals

- ④ Increased urinary excretion
 - citrate,
 - *4-hydroxy-benzeneacetic acid*,
 - *4-hydroxyphenyl-propionic acid*,
- ④ Decreased endogenous metabolites
 - butanedioic acid,
 - benzeneacetic acid,
 - glycine,
 - *4-methyl-phenol*,
 - hippuric acid,
 - *phenylacetyl-glycine*.

区别癌前病变动物和健康动物的关键细菌

Key gut bacteria for differentiation between healthy and precancerous animals

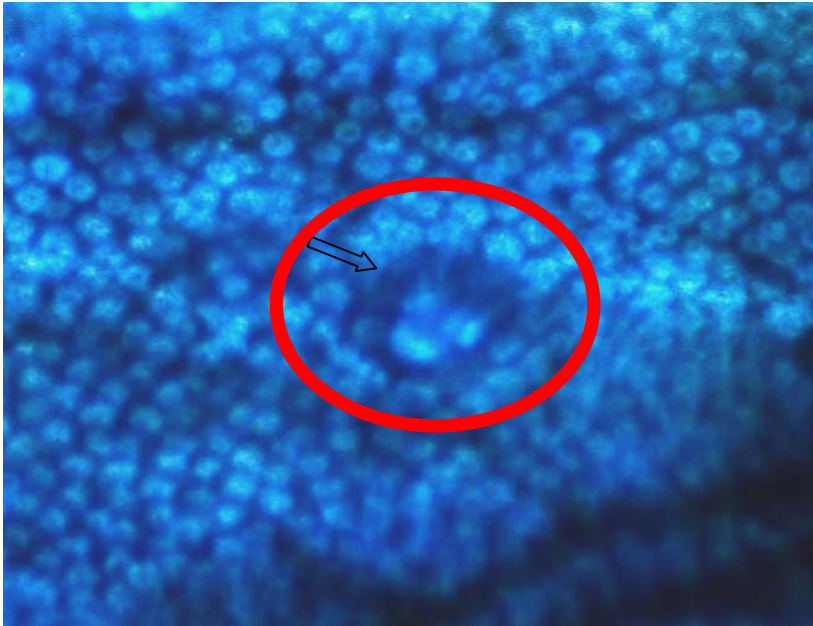
Band		Closest relative	
No.	Similarity (%)	Organism (Acession no.)	Phylogenetic affiliation
19	98	Ruminococcus obeum (AY169419)	Firmicutes;Clostridia;Lachnospiraceae
25	95	Allobaculum stercoricanis(AJ417075)	Firmicutes; Mollicutes; Allobaculum.
26	97	uncultured bacterium(AY986052)	Bacteroidetes;Porphyromonadaceae
	93	Allobaculum stercoricanis(AJ417075)	Firmicutes; Mollicutes; Allobaculum.



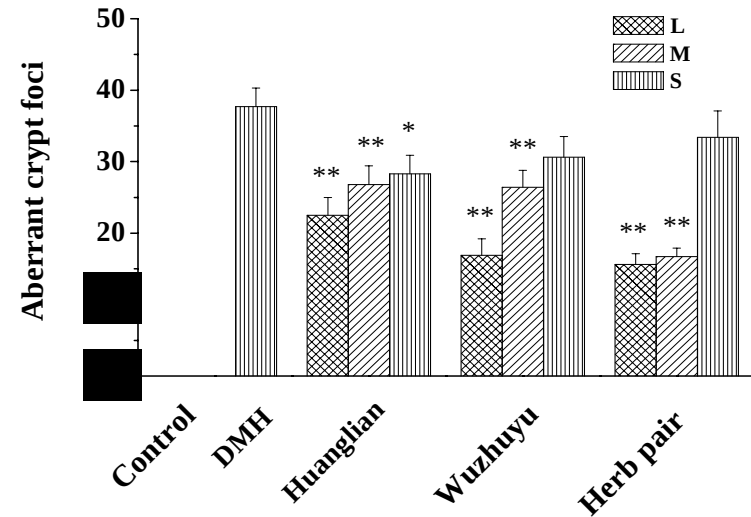
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结肠癌的癌前病变模型 Precancerous lesion of colon cancer



Aberrant crypt foci (ACF) induced by 1,2-dimethylhydrazine (DMH)



Reduction of ACF formation by TCM herbal extracts

Wu group, Jia group, Zhao group

Coptidis rhizoma, *Evodia rutaecarpa* herbal pair

Coptidis Rhizoma



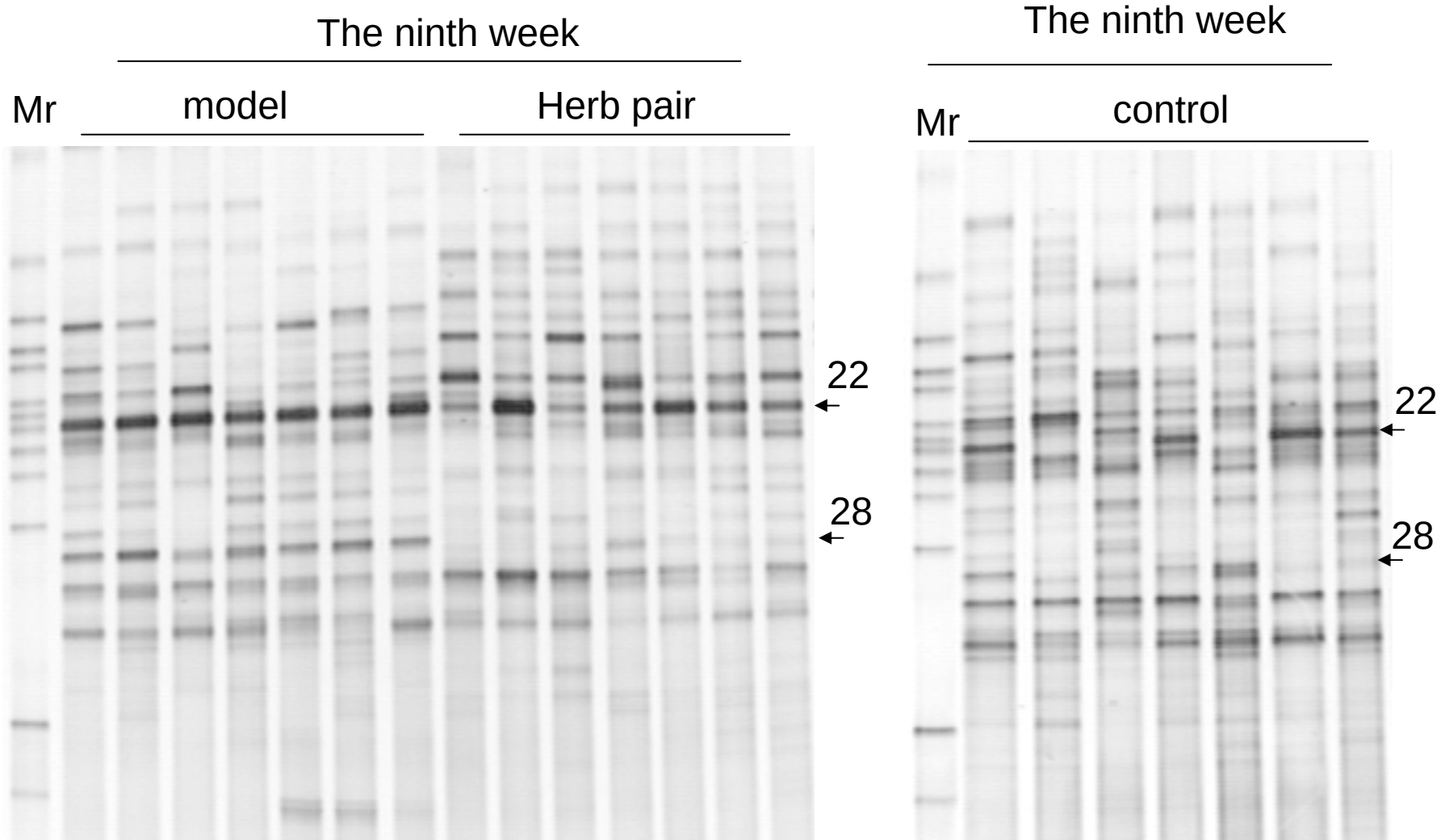
Major component: Berberine 、
palmatine、jatrorrhizine、coptisine

Evodiae Fructus

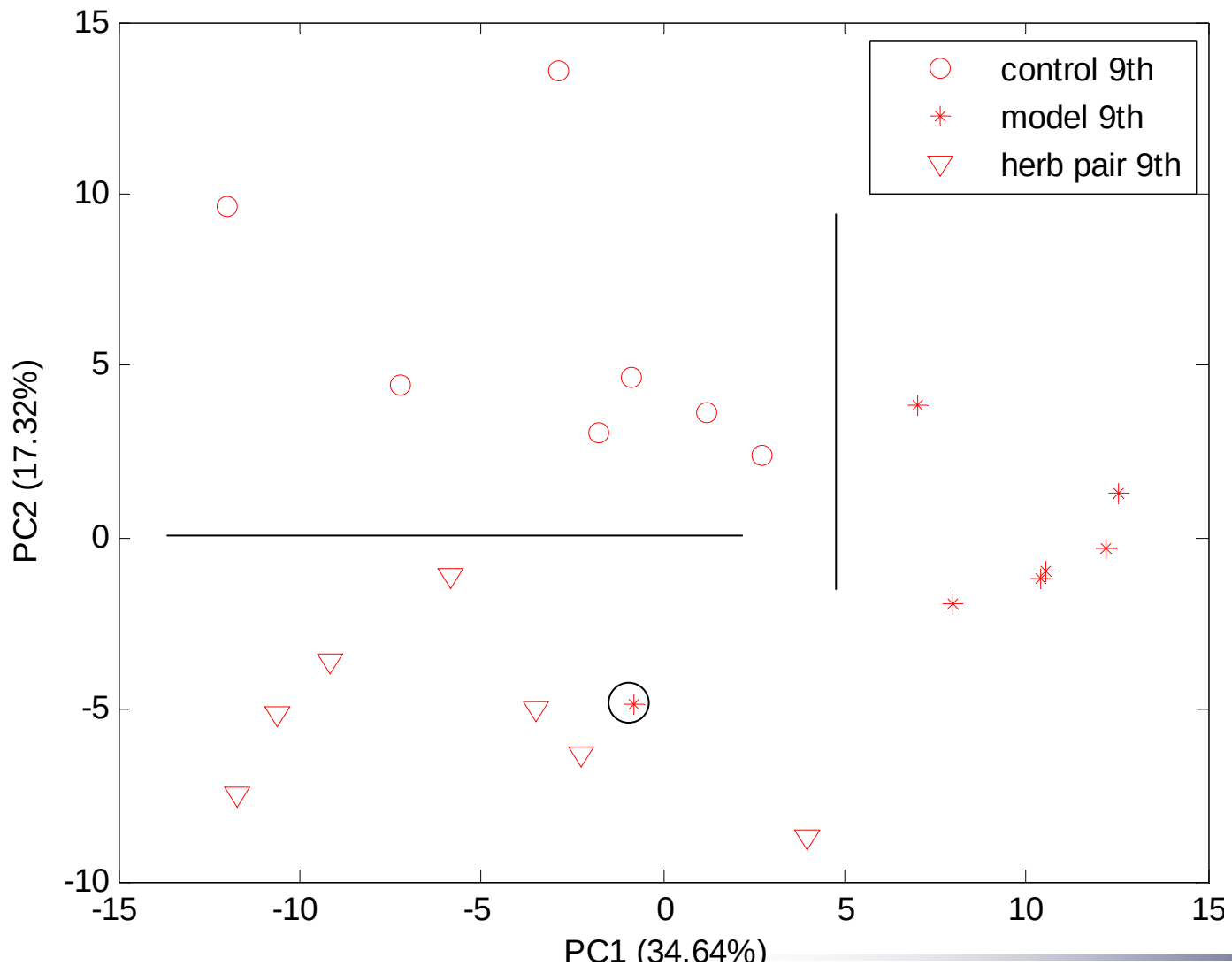


Major component: evodiamine、
rutaecarpine、hydroxy- evodiamine、
limonin、synephrine、evodente

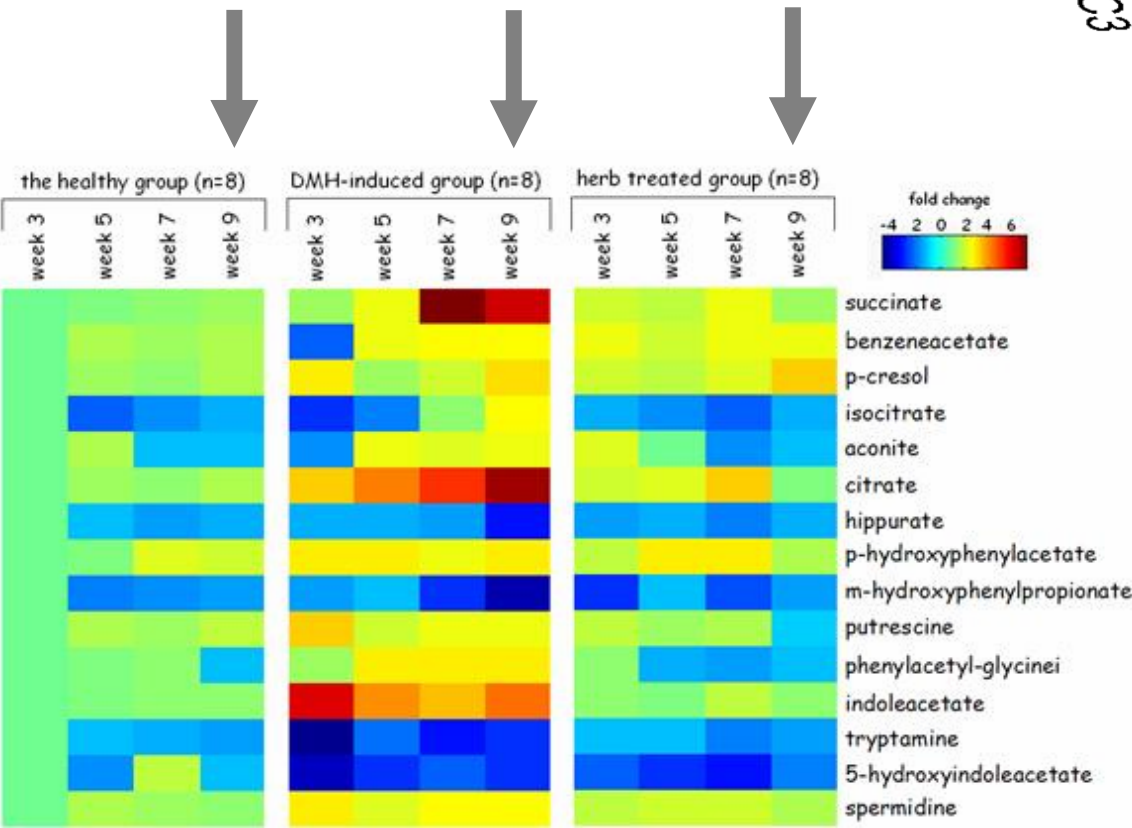
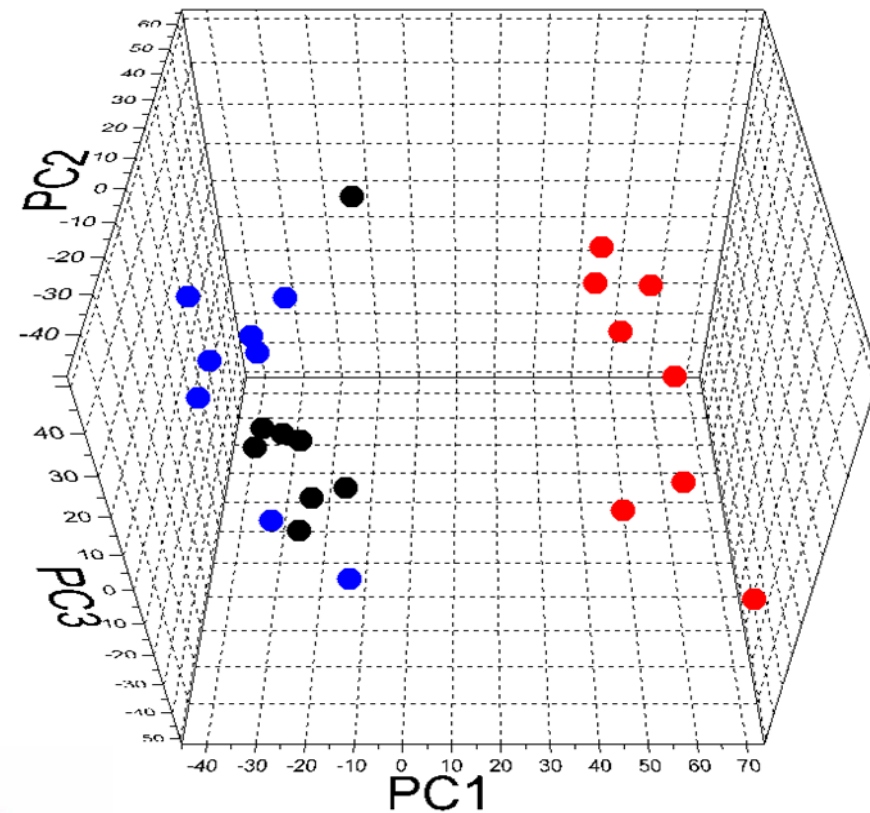
16S rRNA gene V3 fragment DGGE profiles



PCA scores plot of the 16S rRNA gene V3 region DGGE profiles of different groups



A 3D-PCA scores plot of GC/MS spectral data from the three group rats at the 9th week (n=8 per group; DMH-induced, red dots; healthy, blue dots; herb treated, black dots; each dot denotes an individual rat



Time-dependent mean fold changes of those differential metabolites of healthy group, DMH-induced group and herb treated group at 3rd, 5th, 7th, and 9th week .

Jia group

METABONOMICS代谢组学

Quantitative measurement of multivariate metabolic responses of multicellular systems to pathophysiological stimuli or genetic modification

多细胞系统在受到病理生理刺激或者遗传修饰后，其代谢反应的多参数定量测定

AIMS TO MODEL HUMAN GLOBAL METABOLIC REGULATION

-THE BASIC HOLISTIC PHILOSOPHY IS IN HARMONY WITH THEORY OF TRADITIONAL CHINESE MEDICINES

目标是人体整体代谢调控的建模，其基本哲学思想与中医是一致的

GLOBAL SYSTEMS BIOLOGY IS THE TOP-DOWN INTEGRATION OF MULTI-OMICS DATA TO DECIPHER GENE-ENVIRONMENT INTERACTIONS IN RELATION TO DISEASE DEVELOPMENT.

人体系统生物学是用自上而下的策略进行多种组学数据的整合，来解析疾病发展过程中基因与环境的互作关系



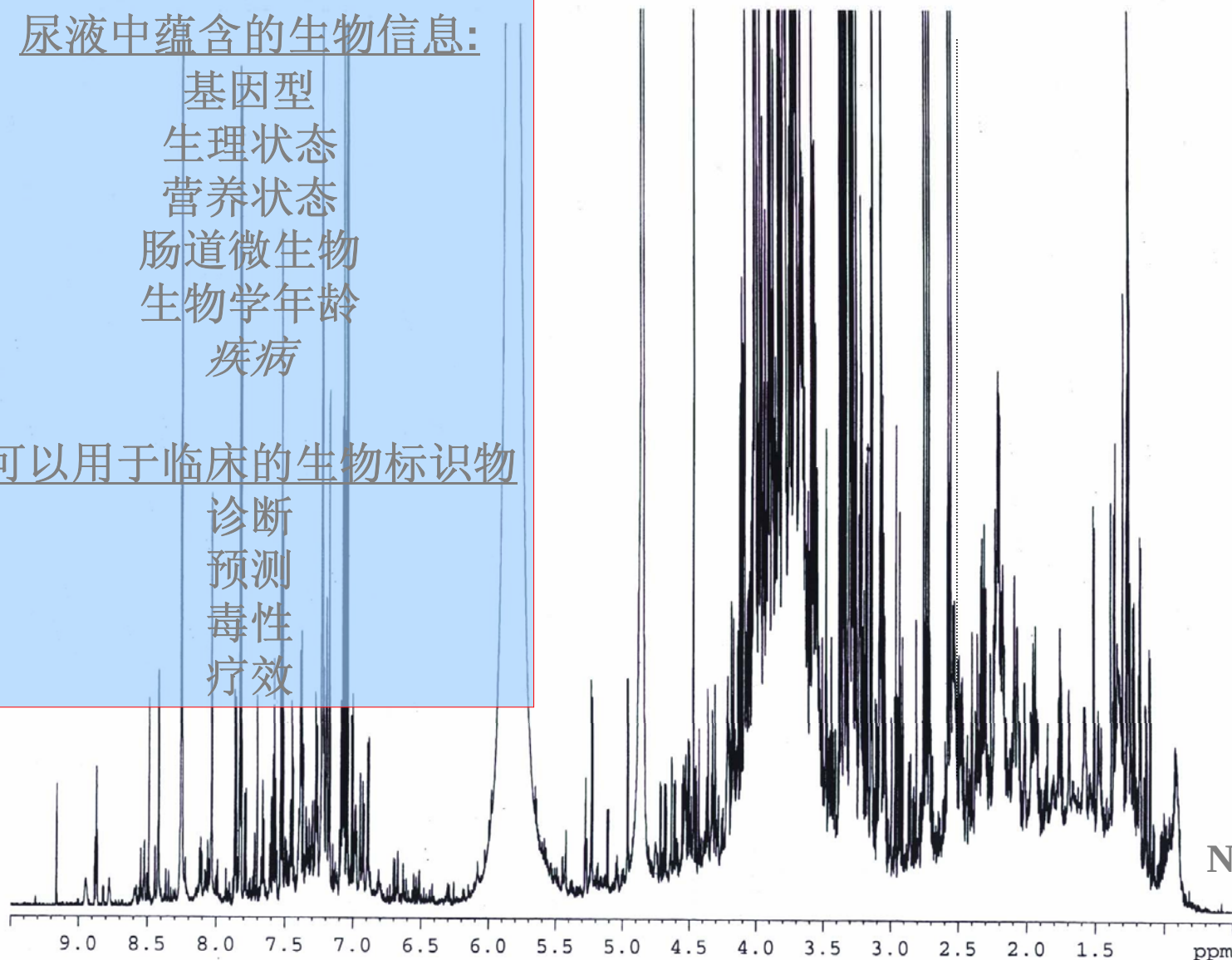
尿液的900 MHz ^1H 核磁共振谱

尿液中蕴含的生物信息:

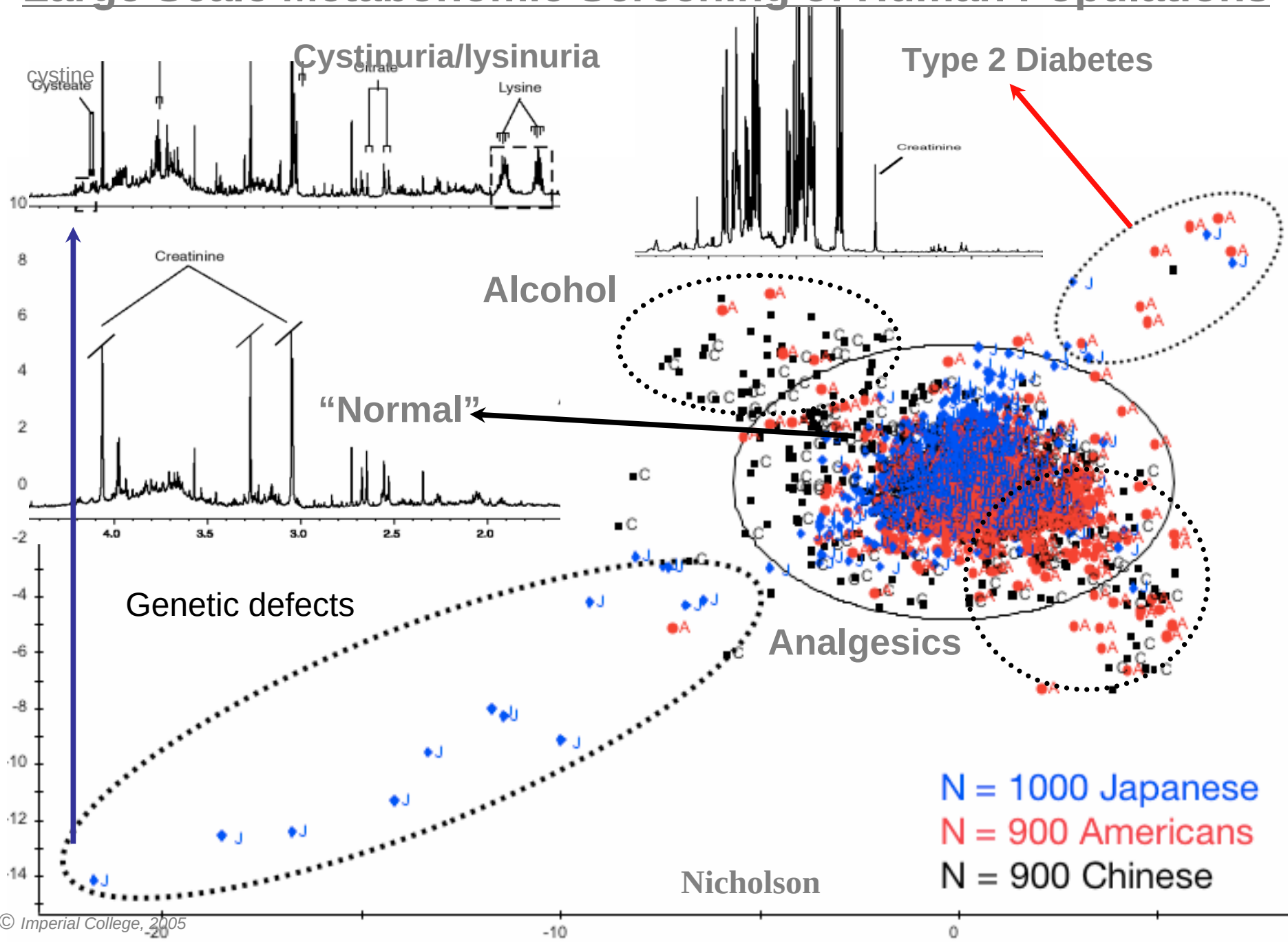
基因型
生理状态
营养状态
肠道微生物
生物学年龄
疾病

可以用于临床的生物标识物

诊断
预测
毒性
疗效



Large Scale Metabonomic Screening of Human Populations



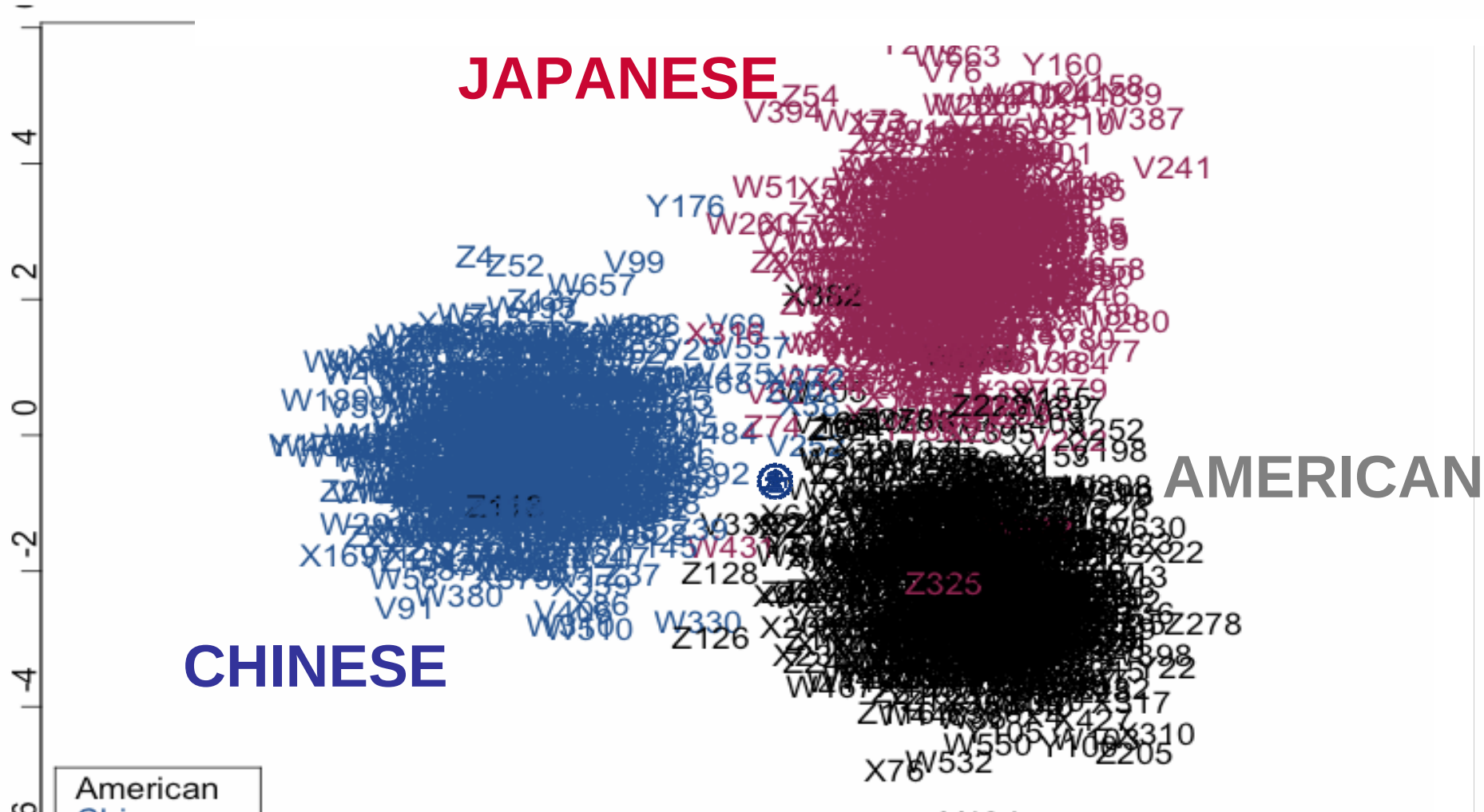


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FUNDAMENTAL METABOTYPE DIFFERENCES

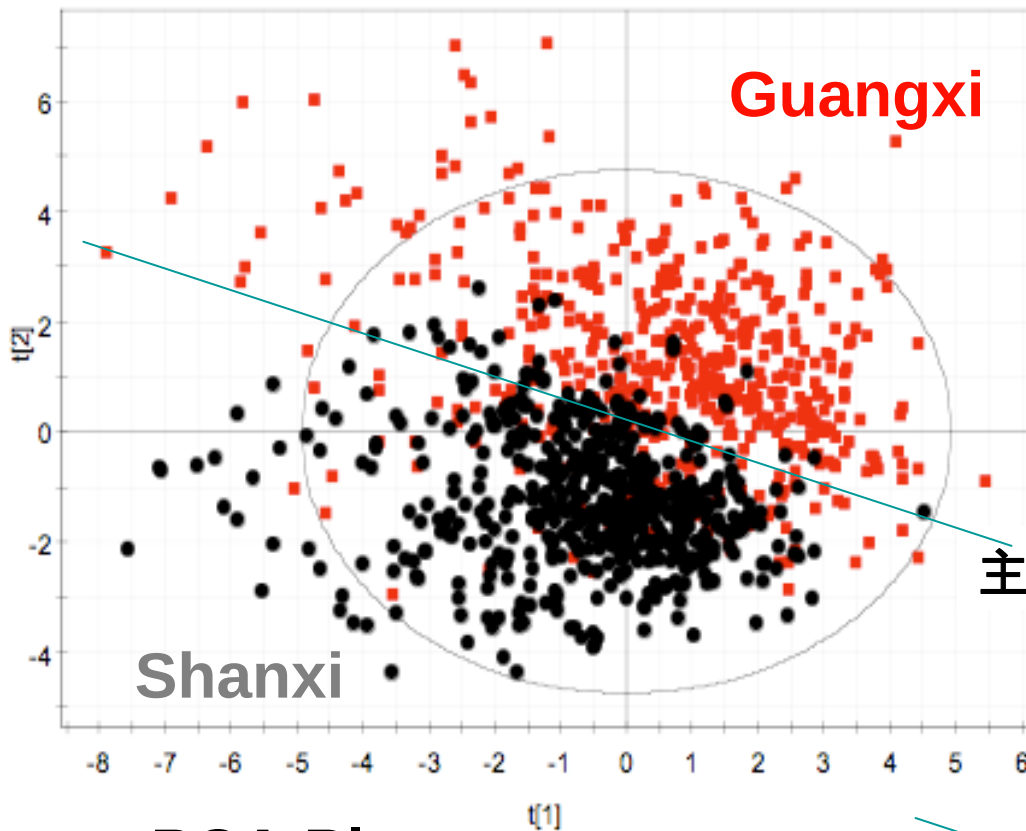
PCA-DA of population data (disease outliers removed)



**COMBINATION OF GENETIC ENVIRONMENTAL
& NUTRITIONAL FACTORS**

Nicholson

NMR-based Metabonomics of south and north Chinese Populations.



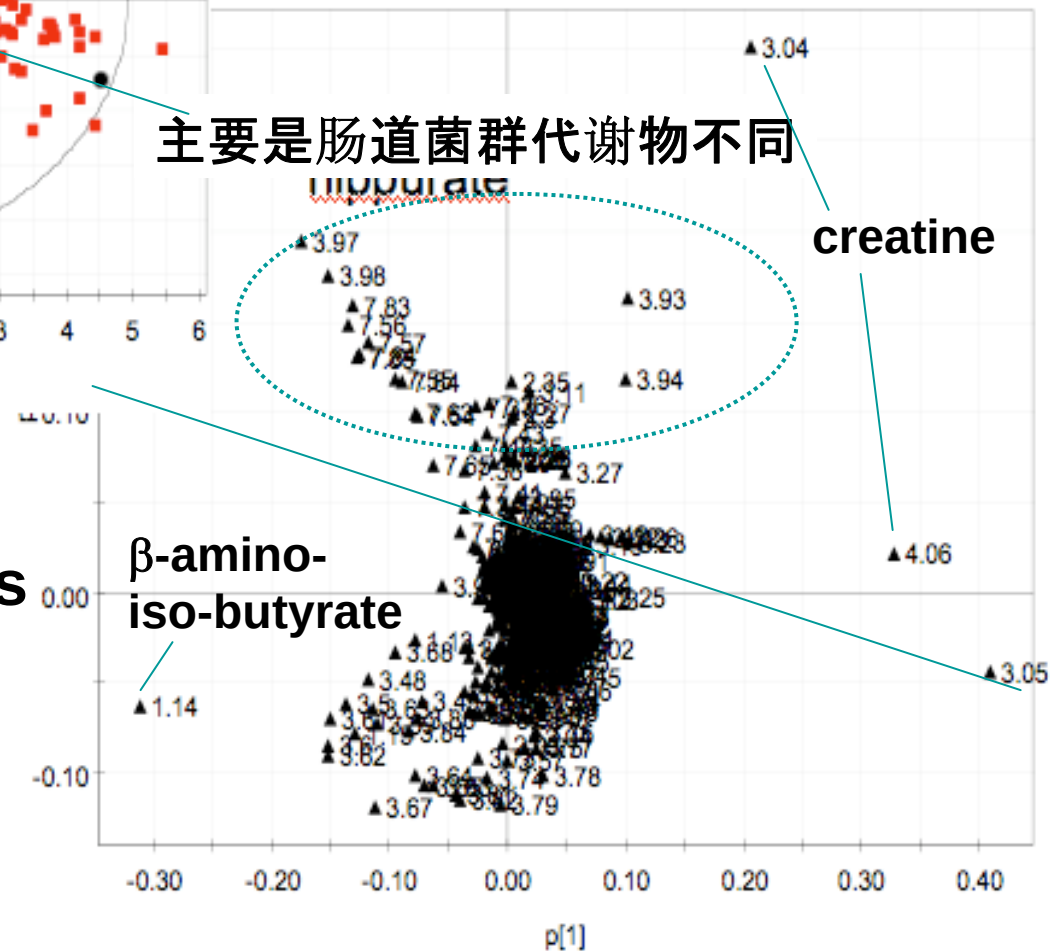
PCA Plot

PCA plot

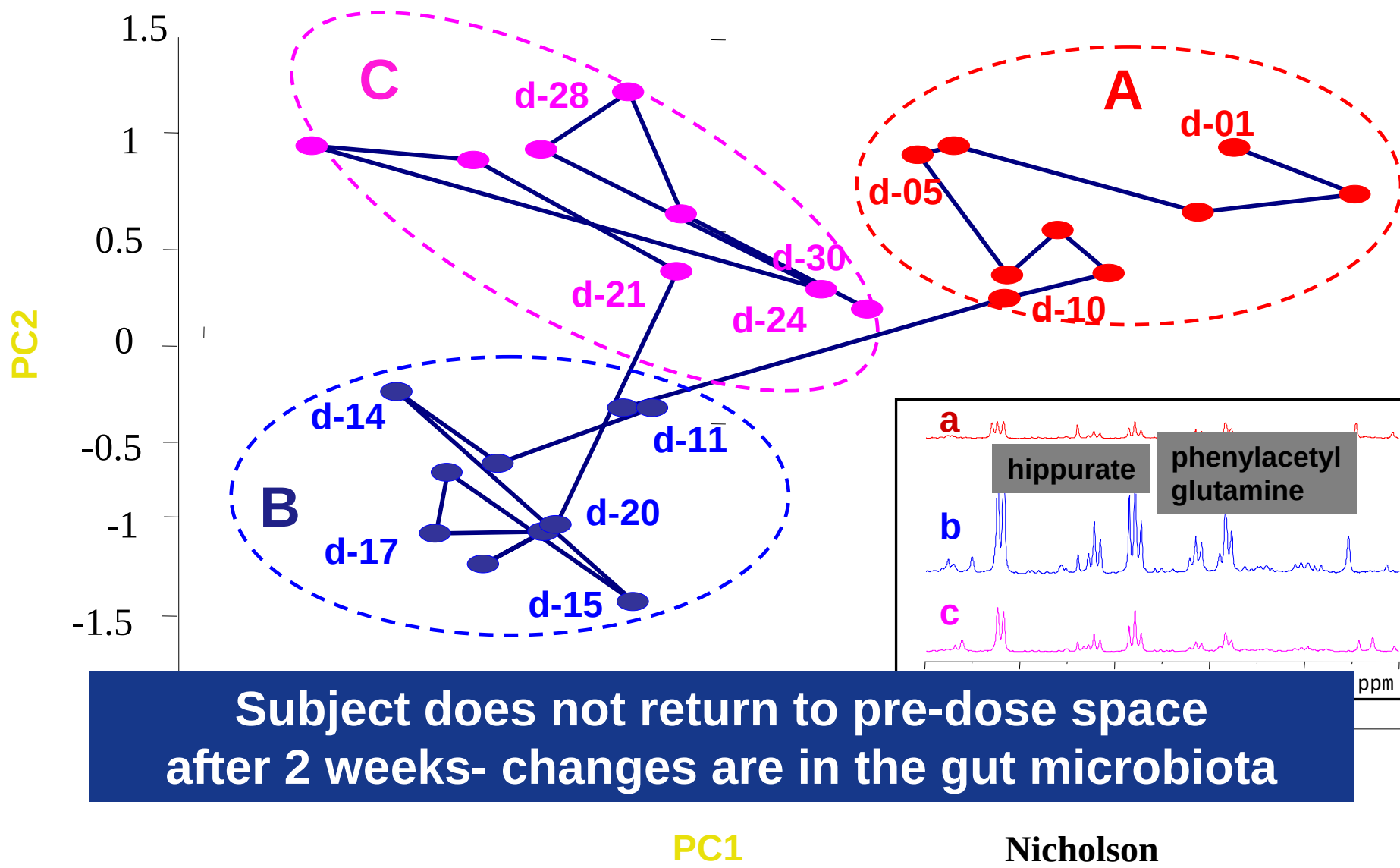
Loadings
plot

Nicholson

主要是肠道菌群代谢物不同



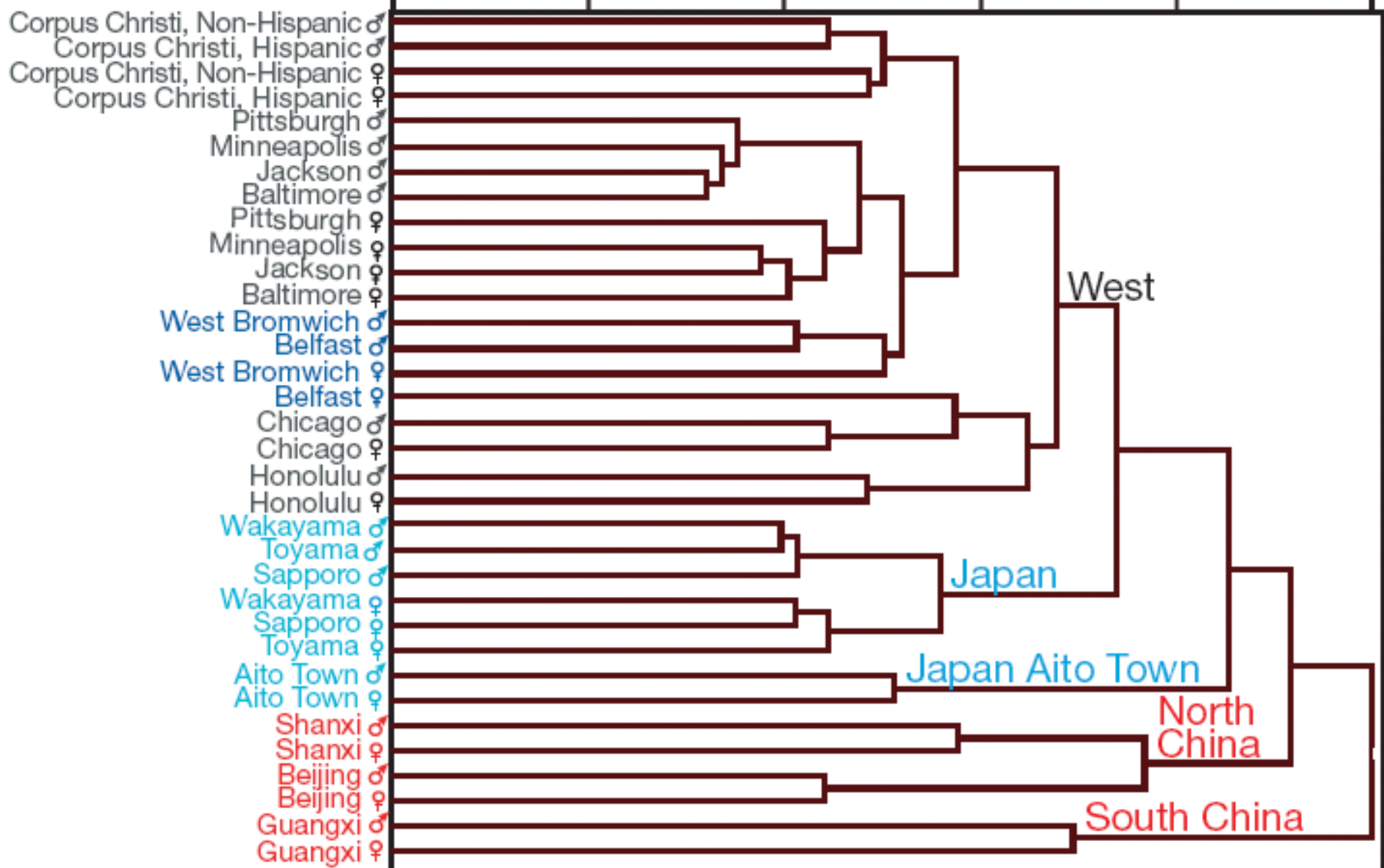
Trajectory plot of OSC-PLS model for individual subject pre and post exposure to chamomile tea



● China ● Japan ● UK ● USA

Similarity index

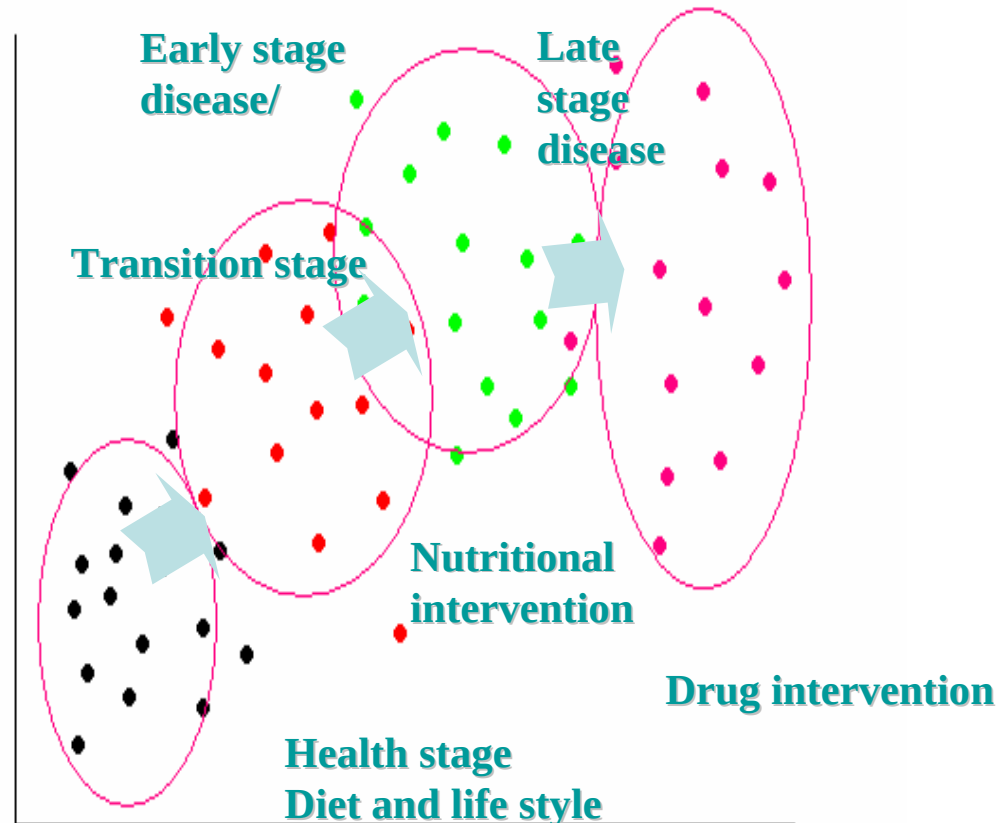
1.0 0.8 0.6 0.4 0.2 0.0



Meta-GUT: Overall Project Aim

Gut Microbiota-based Biomarker Discovery for Preventive Management of Metabolic Diseases via Nutritional Modulation

- ⦿ Nutrition, gut microbiota, host immunity and metabolism, and their interactions in the development of obesity and related metabolic diseases
- ⦿ Opening novel avenues to combat these conditions in a predictive, preventive and personalized manner



Population-based Case-Control Study

Study design:

500 pairs of age, sex and lifestyle matched overweight/obese and non-obese individuals

- Case: BMI ≥ 26 kg/m²
- Control: $18 \leq \text{BMI} \leq 23$ kg/m²

Inclusion criteria:

- Urban residents in Shanghai
- Residence ≥ 10 yrs
- Age: 35-54, male $> 40\%$
- Without currently participating other study
- Without physical disabilities and mental disorder

Data Collection



Dietary Pattern

FFQ & 24-hr recall

Demographic Information

Name, Gender, Age, Household members, Ethnicity, Marital status, Education level, Occupation, Income

Lifestyle & Health Status

Self-reported health status, Health behavior, Medication, Family history of diseases, Smoking status, Alcohol Drinking

Physical Activities

Frequency, Duration and Level (IPAQ-short form)

Mental Health

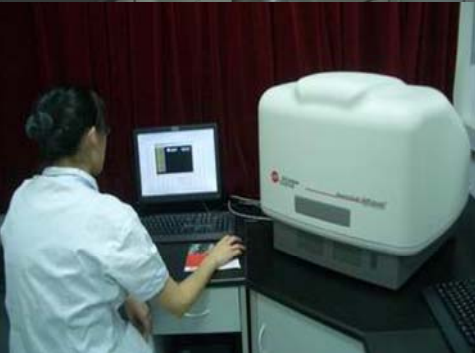
CES-D questionnaire

Anthropometrics Body Composition

Height, Weight, Blood pressure, Waist circumferences, Hip circumferences

DEXA: Fat, lean mass and bone density, % body fat, % trunk fat

Laboratory Assays



Category

Biomarker

Lipid profile

Total cholesterol, HDL, LDL, triglyceride;

Glucose

Fasting plasma glucose

Hormone

Fasting Insulin

Adipocytokines

Adiponectin, Resistin, PAI-1, RBP4

Inflammatory factors

CRP, TNF α -R1,R2, IL-6

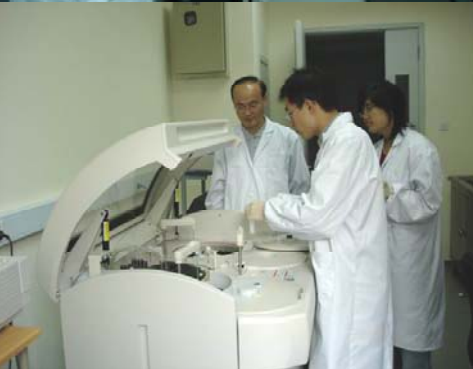
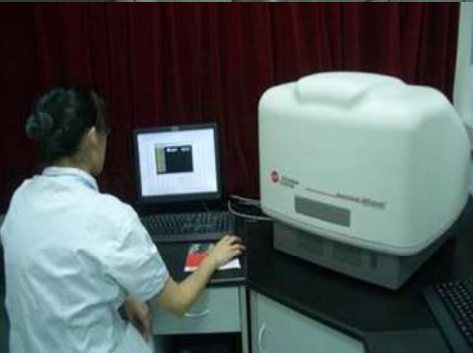
Gene variants

HNF4A, PPARG, PCK1, G6PC, PPARGC1A, NR3C1, ESRRA, ADIPOQ, RBP4, ENPP1,etc.

Others

Ferritin, HbA1C

Laboratory Assays



Samples

Analysis

Blood

Protein profiling

Metabolic profiling

Urine

NMR spectroscopic profiling

MS-based profiling

Fecal matters

Metabolic profiling-fecal water

Fragment-based profiling

Sequence-based profiling

Metagenomic sequencing

Pattern recognition

Unsupervised classification

Supervised classification

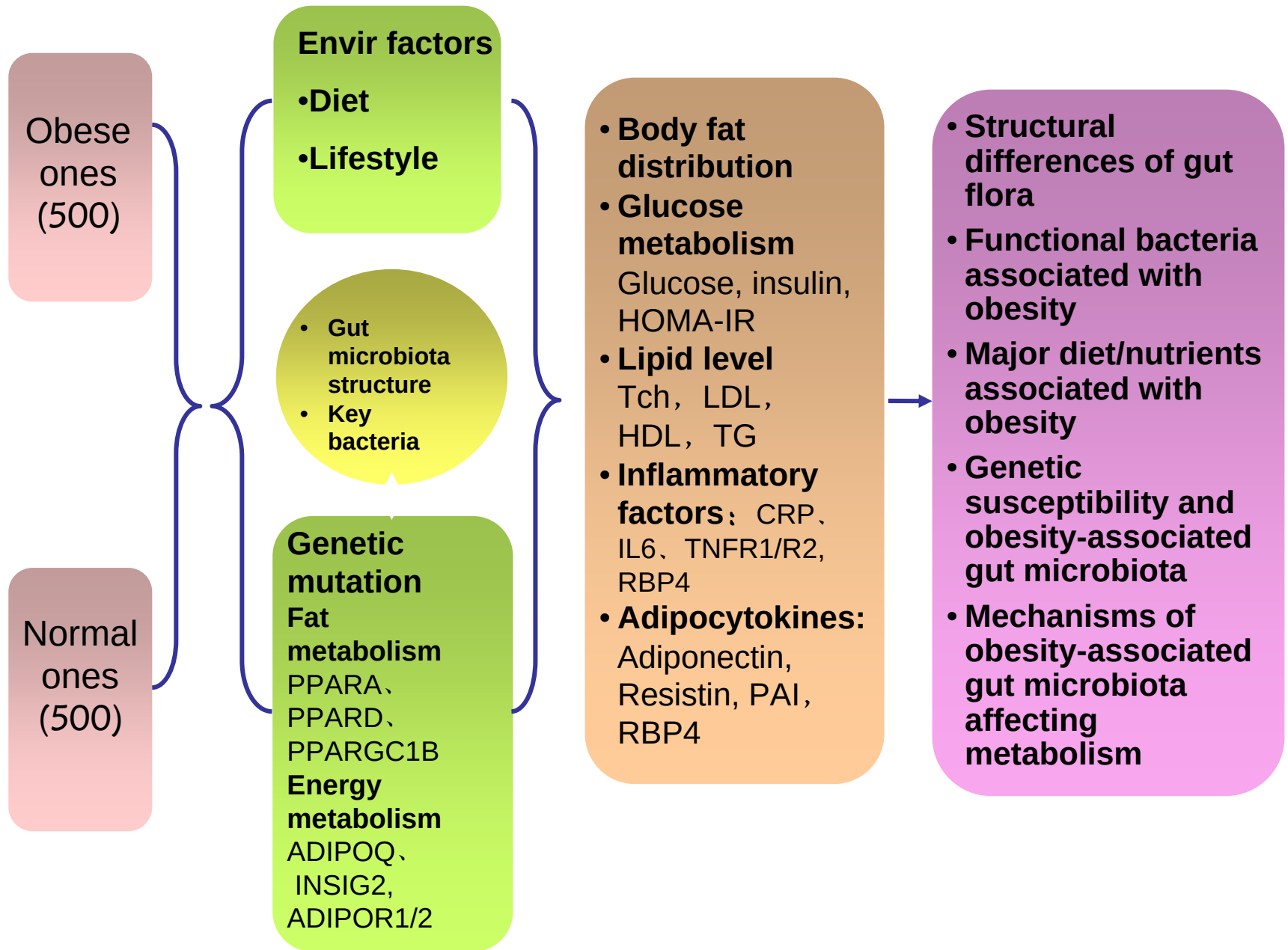
Co-variation analysis

粪、尿液采集情况汇总 Fecal and urine samples

	受试者人数 Number of Participants	合格粪样数量 Fecal samples	合格夜尿数量 Night Urine samples	合格晨尿数量 Morning urine samples
卢湾 Luwan	596	590	581	578
闸北 Zhabei	579	571	568	564
合计 Total	1175	1167	1149	1142

粪尿样均合格者共**1131**人，卢湾**574**人，闸北**557**人

Study Overview



Specific Aims



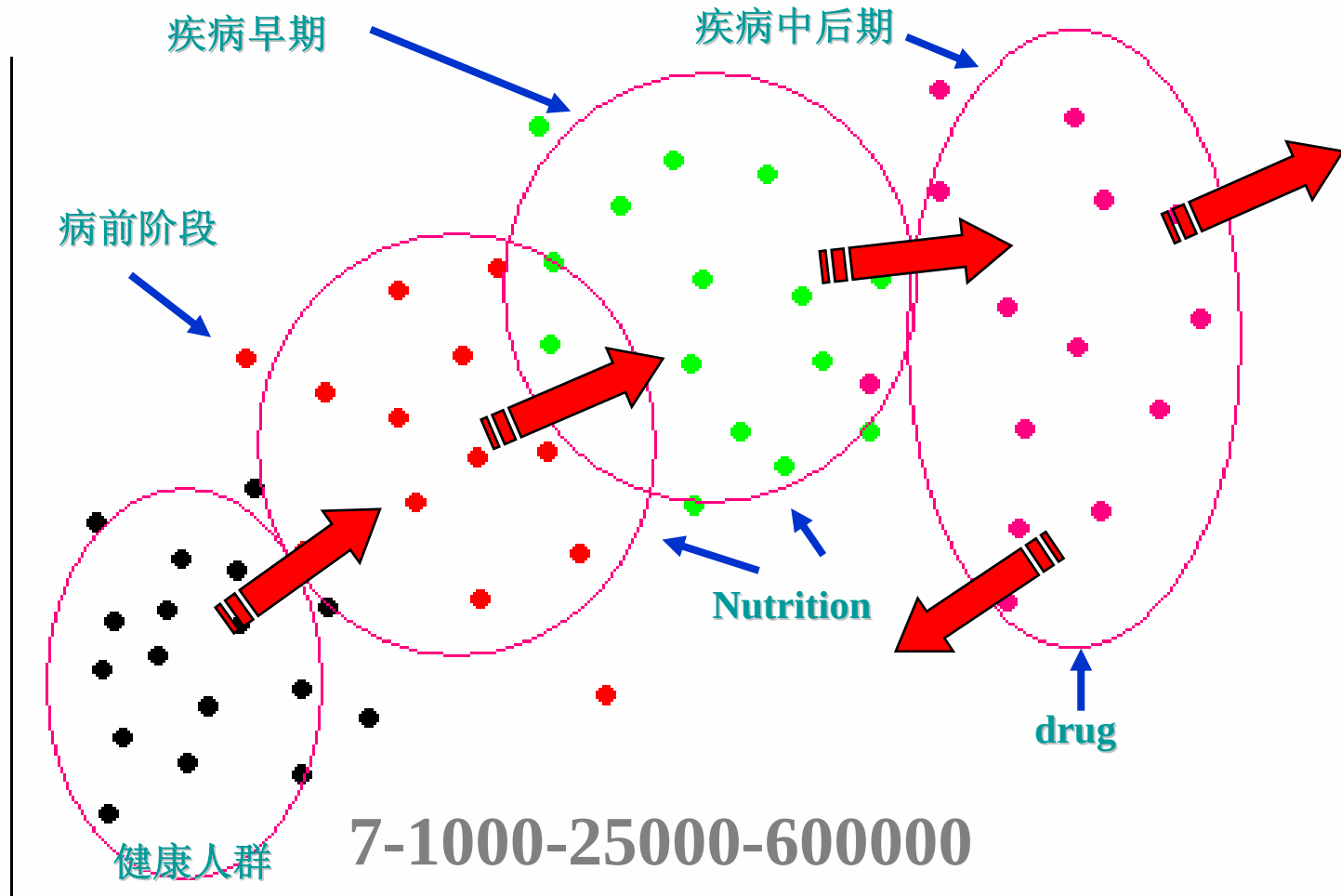
Scientific

- Build a reference database
- Develop high-throughput methodologies
- Define the pattern of nutritional transition
- Identify and understand host-microbe metabolic interactions



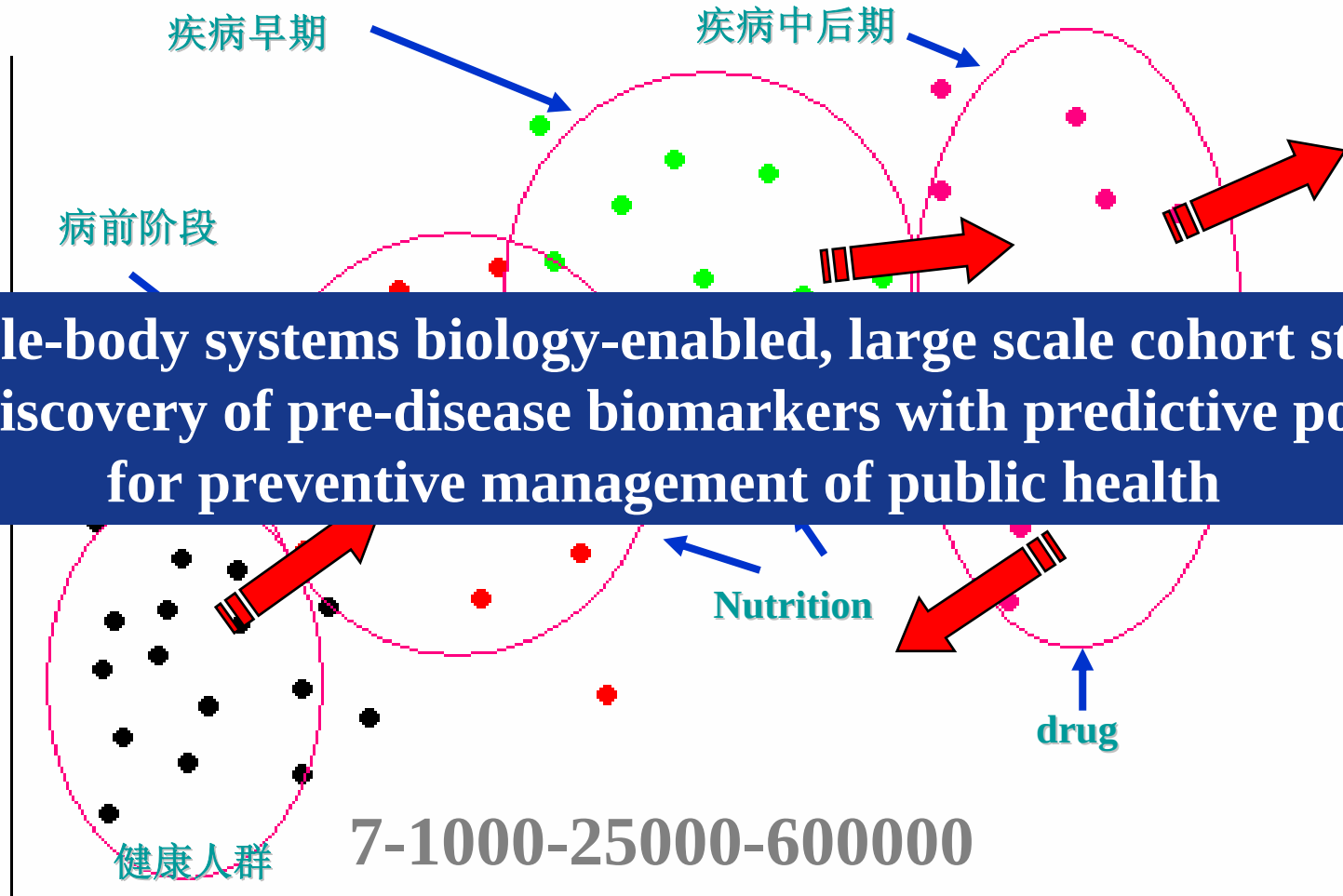
Products for Personalized nutrition

- Health risk assessment
 - Databases and kits
 - Diet-based prevention of metabolic diseases
 - The beverage or additive that works just for you
-



人群健康状况的分类与监测

基于人体分子测量的病人分型与健康监测



Whole-body systems biology-enabled, large scale cohort study for discovery of pre-disease biomarkers with predictive power for preventive management of public health

人群健康状况的分类与监测

基于人体分子测量的病人分型与健康监测



Understanding how TCM works

TCM

Signs and symptoms
at the whole body level



Four diagnostic techniques
Wang, Wen, Wen, Qie

四診“望聞問切”



Eight guiding principles
Yin, Yang, Han, Re
Biao, Li, Xu, Shi

八綱“陰陽，表裏，寒熱，虛實”



“ZHENG證” differentiation
for patient stratification



Whole-body systems biology

Urine and
Stool samples



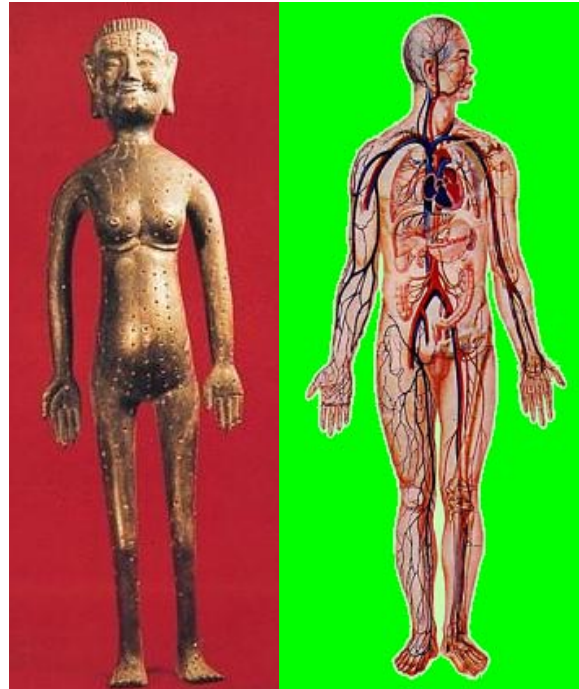
Metabonomics,
Metagenomics



Multivariate statistics
for pattern extraction



“Biomarker profiles”
for patient stratification



Diagnosis and Prognosis,
Efficacy and Safety Evaluation,
Drug Discovery



Cellular and Molecular Mechanisms



Emerging of New Medicine

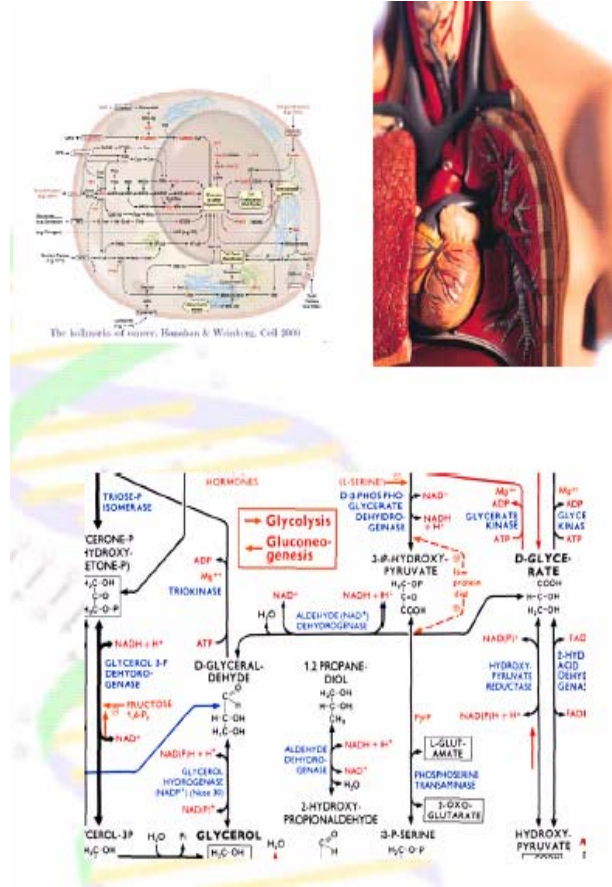
东西方医学的汇聚与新医学模式的出现

Traditional medicine



Holistic but empirical
传统医学—
模糊的整体

Western medicine



Molecular-based but fragmentary
西方医学—
精细的局部

New medicine



Molecular-based and holistic
新医学—
精细的整体