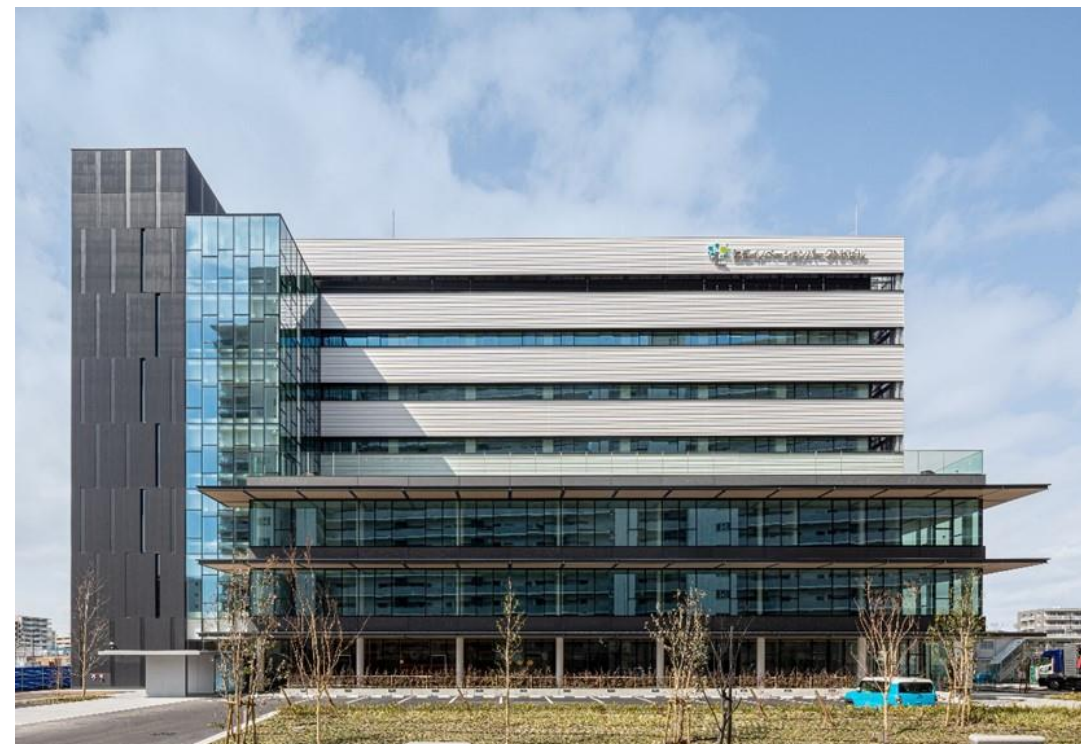
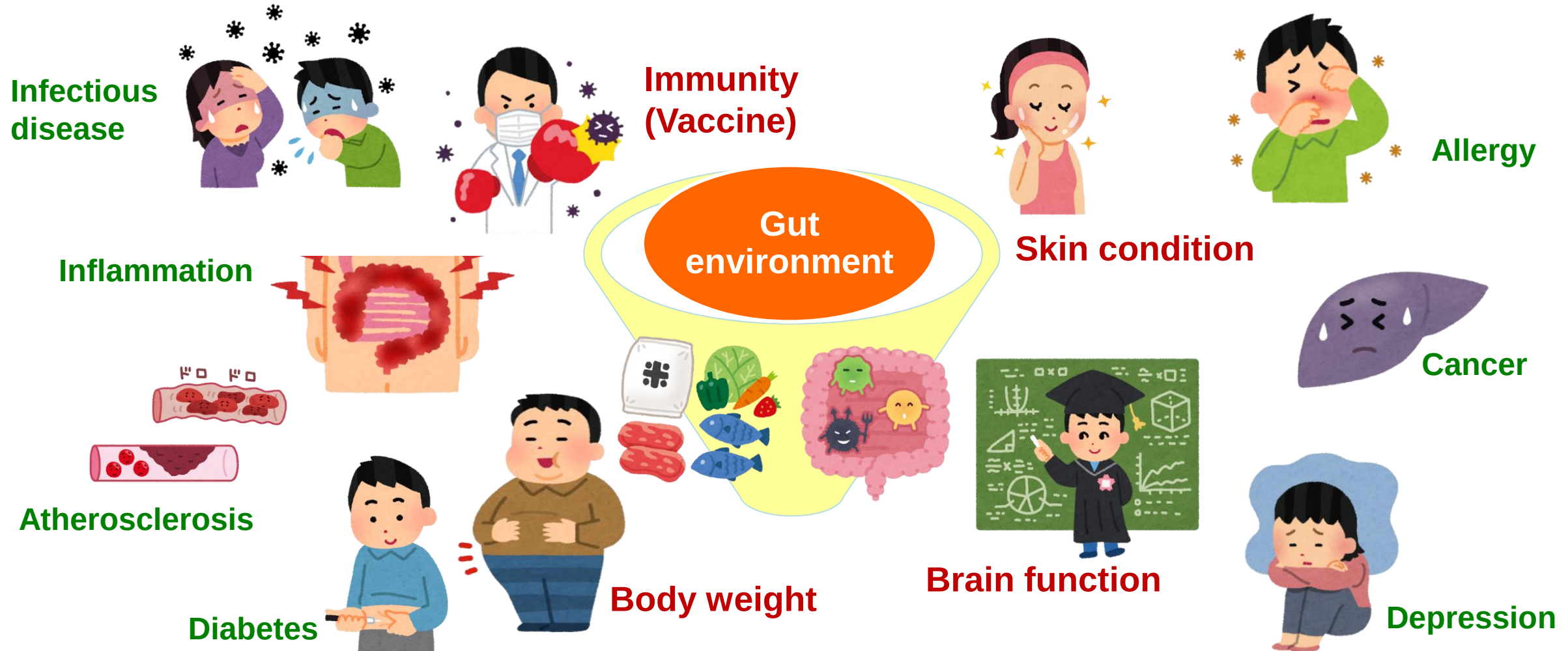


Identification of Beneficial Bacteria in the Japanese Population and its Application to Microbiome Medicines



Control of health and diseases by gut environment

Gut environment (i.e., diet and intestinal bacteria) is related to a variety of health conditions and diseases



Potential of the drug discovery and healthcare industry targeting gut environment₂

Human gut microbiome study@NIBIOHN, Japan

Analyze the characteristics at various area in Japan

Diet Exercise Sleep



匿名化番号	
性別	
年齢	
身長	
体重	
血糖値	
血圧	
中性脂肪含量(骨格筋)	
中性脂肪含量(肝臓)	
アディポネクチン	
レプチン	



Healthy individuals (& patients) at various areas in Japan



Health-related data

Blood



Feces



Saliva



Lifestyle

Diets (BDHQ)
Physical activity
Sleep

Health condition

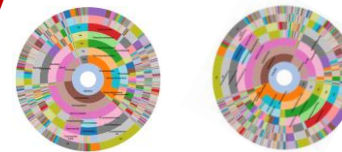
Health checkup
Medical history (disease, medicine)

Items

- (1) Health checkup
- (2) Life style
- (3) Physical activity
- (4) Diseases
- (5) Blood
- (6) Feces
- (7) Saliva
- (8) Others

Database

Microbiome



Metabolome

NIBN JMD
(Japan Microbiome Database)



<https://microbiome.nibn.go.jp/>

Immunity

Antibody (vaccine),
Cytokines etc...

Bioinformatics analysis

Collect data and samples from about 15,000 samples

Database construction and development of user-friendly integrated analysis platform

NIBN Collaboration with Prof. Kenji Mizuguchi (NIBN)

In addition to raw data of intestinal bacterial data, NIBIOHN JMD includes information (NOT raw data) of 1,640 items related to health/disease and lifestyle habit, metabolites, and other biological molecules

NIBN JMD

(Japan Microbiome Database)

<https://microbiome.nibn.go.jp/>

腸内細菌叢データベースで新たな健康社会を実現

MANTA Microbiota And pheNotype correlaTion Analysis platform

Microbiome

FASTQ file

Data processing pipeline creation,
automation of the whole process

- FASTQ file trimming
 - Trimming pair-end sequence
 - Remove too short sequence
 - Remove PCR primer sequence
 - Remove sequence included PhiX control sequence
 - Remove sequence included Adapter sequence
 - Merge Forward sequence and Reverse sequence
 - Remove Chimera sequence
 - Quality check
- Analysis of Microbiome
 - Make Mapping file
 - OTU picking
 - OTU Alignment
 - OTU Assignment
 - Make Biom file
 - Make rep set file
 - Pick up 10,000 reads randomly
 - Alpha diversity analysis
 - Beta diversity analysis

Microbiota
data

NIBIOHN



Database

MANTA interface

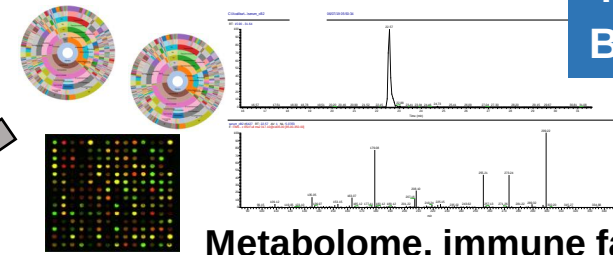
Immunity
Lifestyle
Physiological
⋮

Data of lifestyle and
medical examinations

Unification of terms
and concepts



Metabolites and
Biological factors



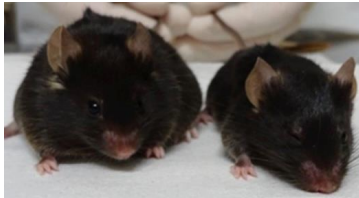
Metabolome, immune factors, etc.

Integrated analysis platform

Not only to store data, but also data
visualization and analysis

Relationship between intestinal bacteria and obesity

The nature of obesity is transmitted with intestinal bacteria

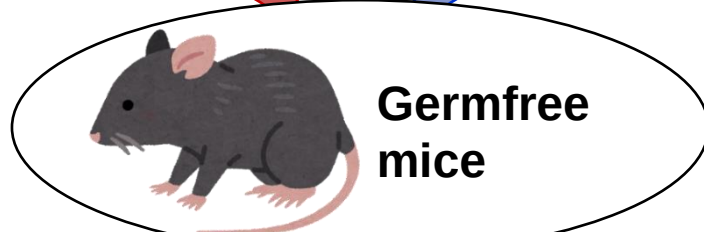


Obese humans and mice

Non-obese humans and mice



Administration



Germfree mice



Increased body weight



No change

Euro

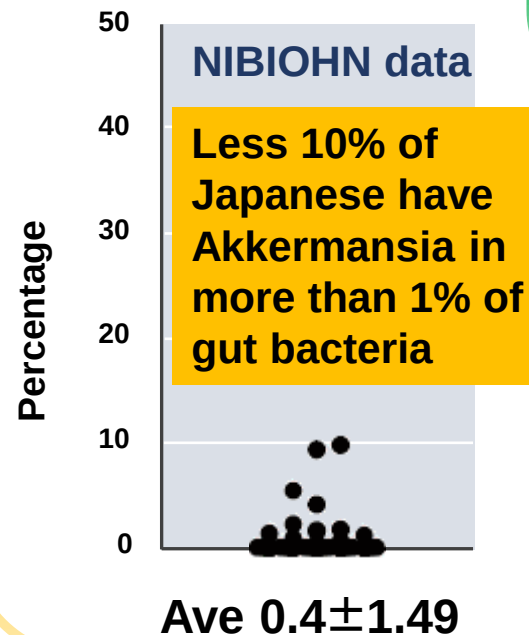
> EFSA J. 2021 Sep 1;19(9):e06780. doi: 10.2903/j.efsa.2021.6780. eCollection 2021 Sep.

Safety of pasteurised *Akkermansia muciniphila* as a novel food pursuant to Regulation (EU) 2015/2283



Akkermansia for weight management:
EFSA approves A-Mansia Biotech's next-gen bacterium

Japanese



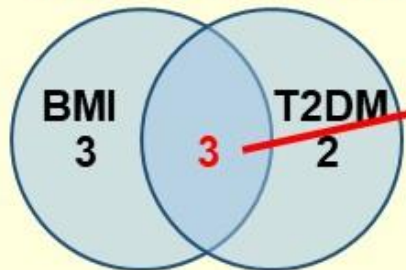
Akkermansia muciniphila is rare in Japanese



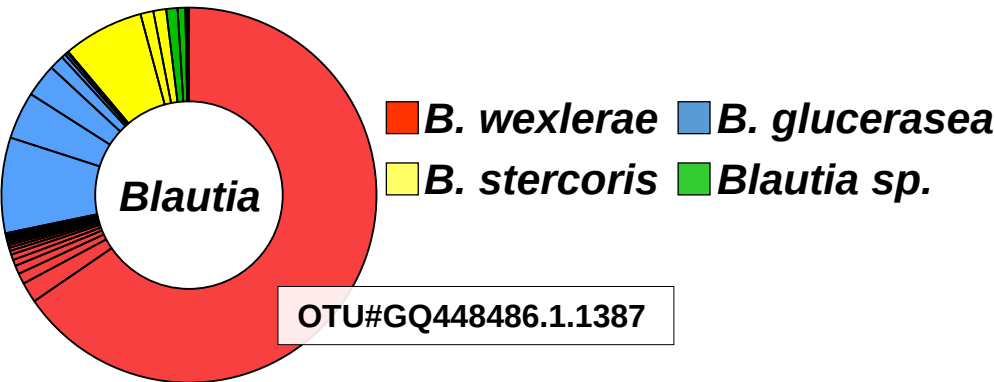
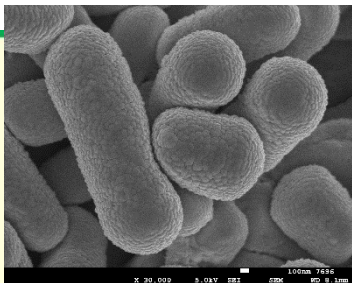
A possibility of presence of unique bacteria to control body weight in Japanese?

Identification of *Blautia* as a candidate to improve obesity and diabetes in Japan

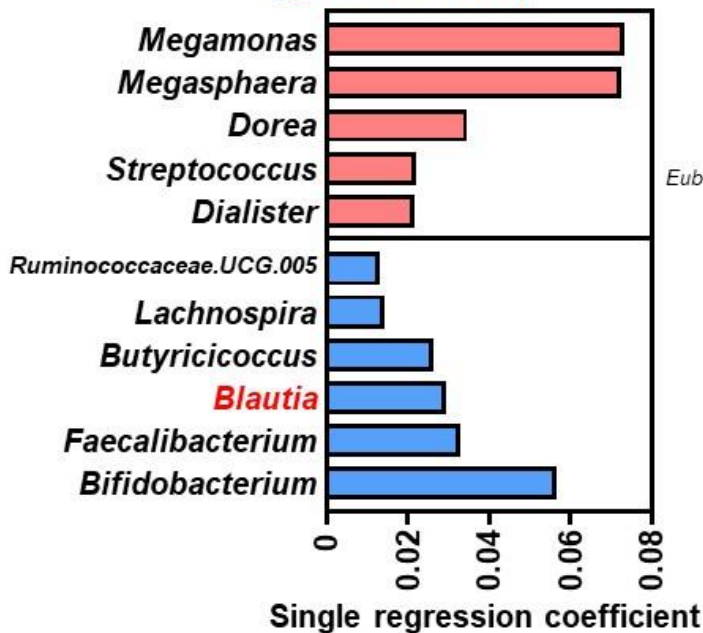
Blautia wexlerae is abundant in non-obese (left) or non-diabetic (right) individuals



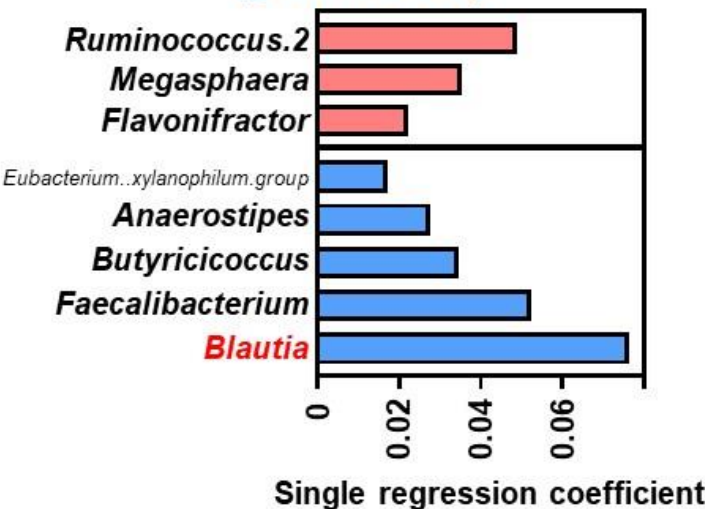
Blautia
Butyricicoccus
Faecalibacterium



BMI-related bacteria
(genus, >0.1%)

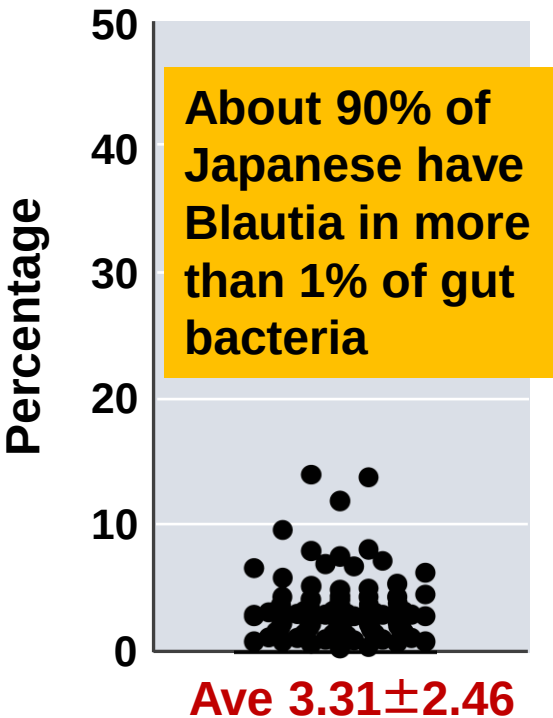


T2DM-related bacteria
(genus, >0.1%)

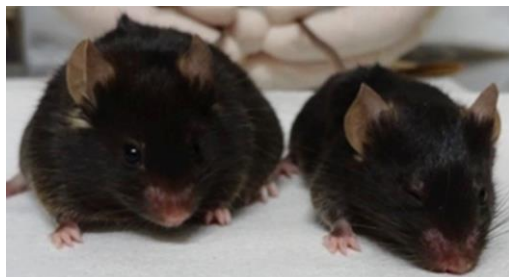


■ Positively related
■ Inversely related

NIBIOHN data



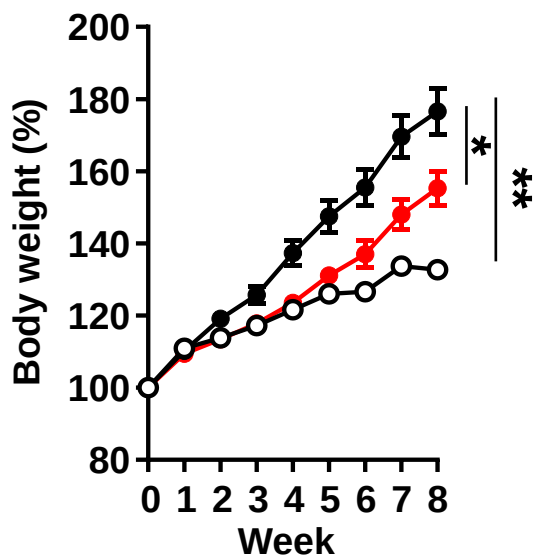
Production of Metabolism-boosting, Anti-Inflammatory, and Gut-Improving Substances by *Blautia wexlerae* with Benefits in Obesity and Diabetes Models



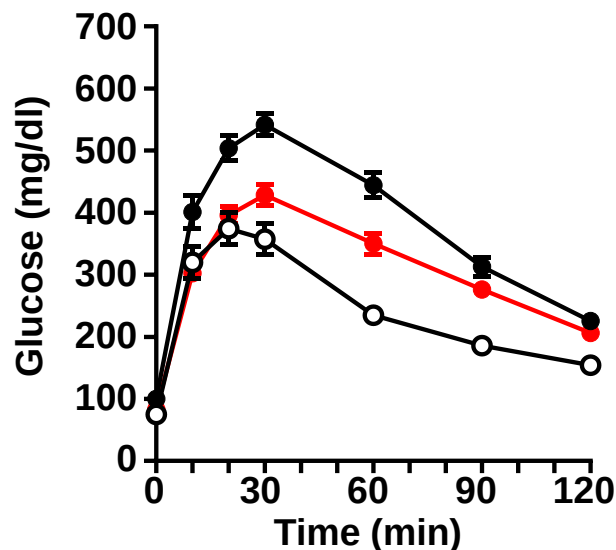
High fat

Normal

Body weight



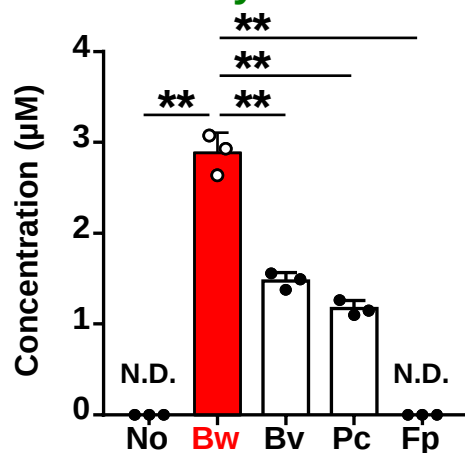
Diabetes



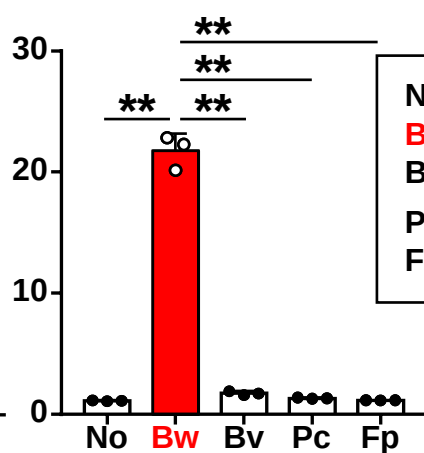
○ Normal ● High fat ● High fat + Blautia

Metabolomic Analysis

S-adenosylmethionine



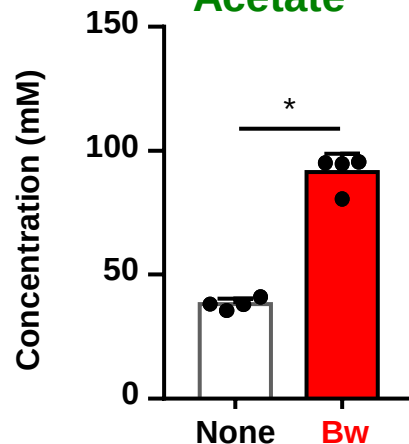
L-ornithine



No: Medium only
Bw: *Blautia*
Bv: *Bacteroides*
Pc: *Prevotella*
Fp: *Faecalibacterium*

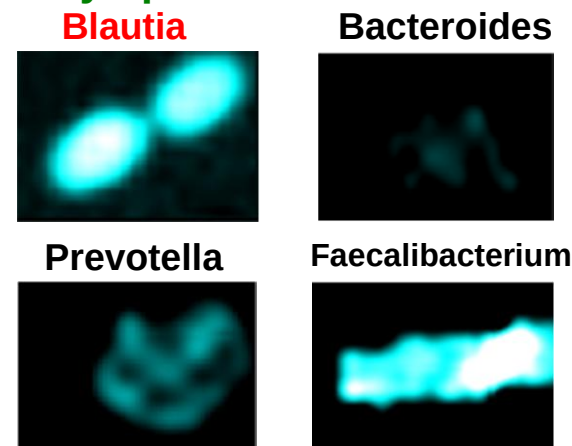
SCFA

Acetate



Raman analysis

Amylopectin



Takeyama's group (Waseda U)

Anti-obesity and Anti-inflammatory Mechanisms of *Blautia* and Future Plans

nature communications

2022.08.18

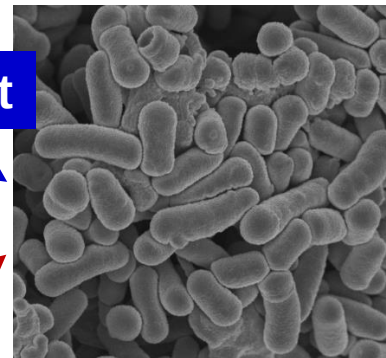
Article

<https://doi.org/10.1038/s41467-022-32015-7>

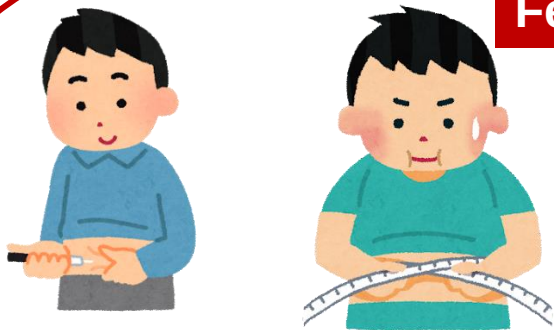
Oral administration of *Blautia wexlerae* ameliorates obesity and type 2 diabetes via metabolic remodeling of the gut microbiota



Blautia wexlerae



Few



Diabetes

obesity

Preventing and improving effect on obesity and diabetes

Metabolites for the improvement of diabetes and gut environment

- ✓ S-adenosylmethionine
- ✓ L-ornithine
- ✓ Indigestible starch (amylose, amylopectin)
- ✓ Succinic acid, lactic acid, acetic acid

Mechanism of action

【Direct effect】

Promote lipid metabolism in adipose tissue and liver
Suppress inflammation in adipose tissue

【Indirect effect】

Improvement of the gut environment (e.g. increase in short-chain fatty acids)

Future plans

- ✓ Search for ingredients and others to increase *Blautia*
- ✓ Application to probiotics and **drug discovery**
- ✓ Verifying safety and efficacy in humans
- ✓ Diagnostic system to detect and measure *Blautia*

Practical Application of Microbiome-based Therapeutics

Single strain



Bacterial cocktail



In many studies, ...

1. This single strain (or bacterial cocktail) has therapeutic potential to treat the disease.
2. The efficacy of this bacterium is attributed to its production of XX

Other side effects and safety profiles remain unknown

Establishment and validation of testing methods related to quality, efficacy, and safety to support therapeutic targets and mechanisms of action

Selection of best strains

- Efficacy (Mechanism of Action)
- Adverse reactions and side effects
- Safety (e.g., toxin production, antibiotic resistance)
- Phages, plasmids, and other mobile genetic elements

Production, formulation, and Supply Chain

- Culture system
- Scale-up
- Stability
- Formulation (e.g., lyophilization, capsules)

For preclinical test

- PK/PD markers
- Biodistribution (bacterial translocation)
- Necessity of 16S rRNA and metagenomic analyses for efficacy evaluation

Defining regulatory requirements and quality standards

Project Focused on Developing Key Technology for Discovering and Manufacturing Drugs for Next-Generation Treatment and Diagnosis

- 1. Technology Development and Infrastructure Building for MB Drug Discovery**
MB創薬に関わる技術開発及び基盤構築
- 2. Advanced Fundamental Technologies through Application of Microbiome Modulation Techniques for Intestinal Immunity-Related Diseases**
腸管免疫関連疾患に対するMB制御技術応用による基盤技術の高度化
- 3. Development of Non-clinical Pharmacology, Pharmacokinetics, and Toxicological Evaluation Techniques for Clinical Application of Bacterial Preparations Controlling the Microbiome**
MBを制御する菌製剤の臨床応用に向けた非臨床薬理、薬物動態及び毒性学的評価技術の開発
- 4. Development of Manufacturing and Quality Control Techniques for Bacterial Preparations Controlling the Microbiome**
MBを制御する菌製剤の製造、品質管理技術の開発
- 5. Development of Advanced Microbiome Modulation Technologies Targeting Gut Bacteria Contributing to Disease Control**
疾患克服に資する腸内細菌を標的とした先端的MB制御技術の開発

Development of evaluation technologies for nonclinical pharmacology and ADMET of microbiome-based medicine



Co-PI (Kobe Univ)
Akihiko Kondo



In Vitro Human
Gut Microbiota
Model



Co-PI (AIST)
Yuji Sekiguchi



Microbiological
Evaluation by
Bioinformatics



PI (NIBN)
Jun Kunisawa



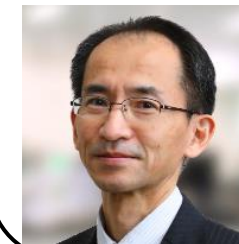
Animal Model
and Human Data



JMBC
一般社団法人日本マイクロバイオームコンソーシアム



Co-PI (The Univ of Osaka)
Masuo Kondoh



Pharmaco-
microbiomics
Analysis



Co-PI (The Univ of Osaka)
Hiroyuki Mizuguchi



iPS- or Organoid-
based Epithelial
Cell Function