14th APAC

2025.04.22
@Keidanren Kaikan, Tokyo

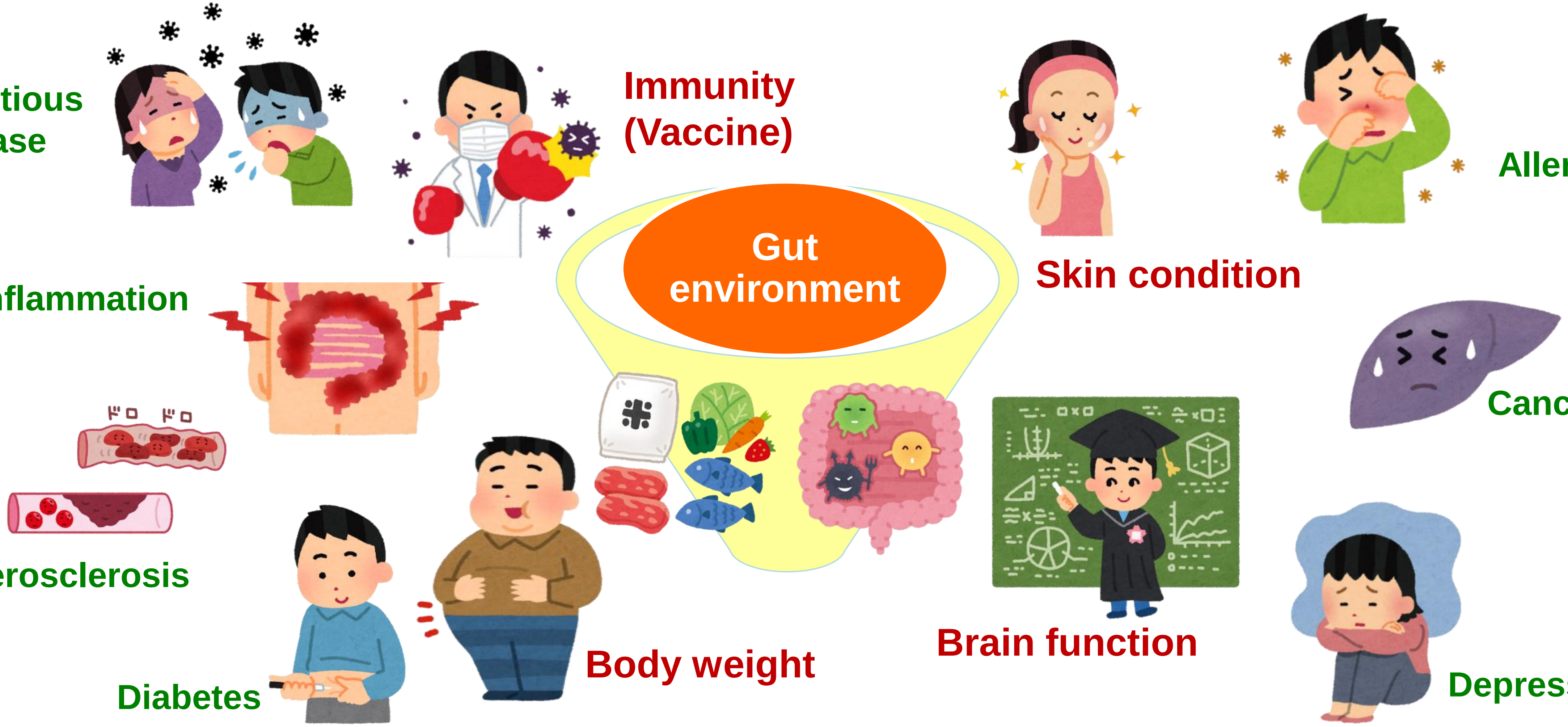
Identification of Beneficial Bacteria in the Japanese Population and its Application to Microbiome Medicines

NIBN National Institutes of Biomedical Innovation,
Health and Nutrition (NIBN)

Jun Kunisawa

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



Infectious disease

Immunity (Vaccine)

Skin condition

Allergy

Inflammation

Gut environment

Cancer

Atherosclerosis

Body weight

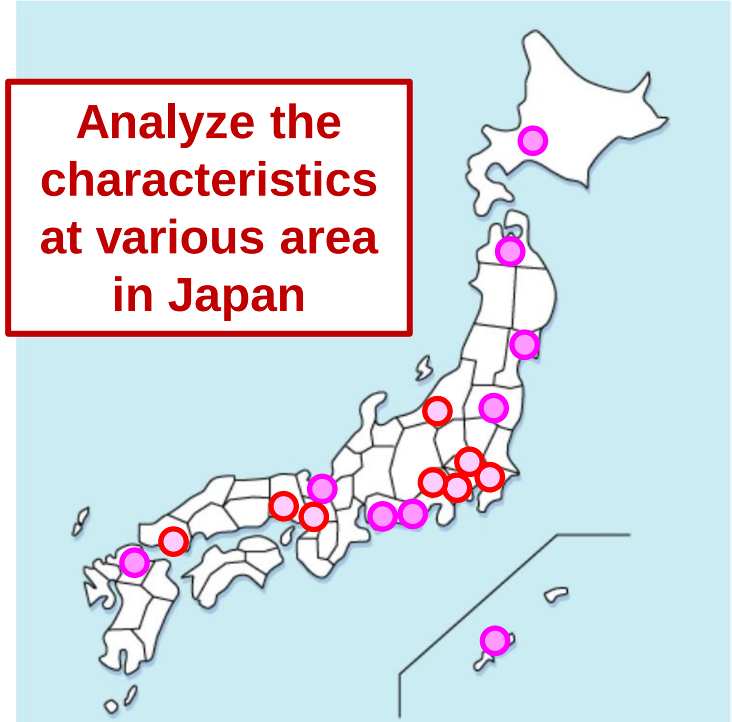
Brain function

Diabetes

Depression

Potential of the drug discovery and healthcare industry targeting gut environment

Human gut microbiome study@NIBIOHN, Japan



Analyze the characteristics at various area in Japan

Collect data and samples from about 15,000 samples

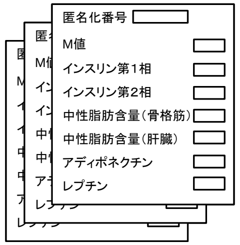
Diet **Exercise** **Sleep**

Health-related data

Blood **Feces** **Saliva**

Items

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



匿名化番号 □
M値 □
インスリン第1相 □
インスリン第2相 □
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

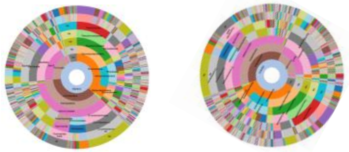
Lifestyle	Health condition
Diets (BDHQ) Physical activity Sleep	Health checkup Medical history (disease, medicine)

NIBN JMD
(Japan Microbiome Database)

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

Database

Microbiome



Metabolome

Immunity

Antibody (vaccine), Cytokines etc…

Bioinformatics analysis

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)

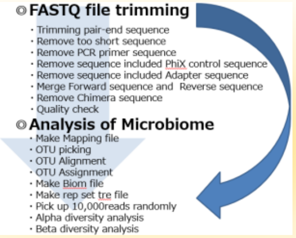
https://microbiome.nibn.go.jp/

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

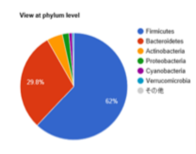
FASTQ file



◎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 tre file
- Pick up 10,000reads randomly
- Alpha diversity analysis
- Beta diversity analysis

Data processing pipeline creation, automation of the whole process



Microbiota data

Data of lifestyle and medical examinations

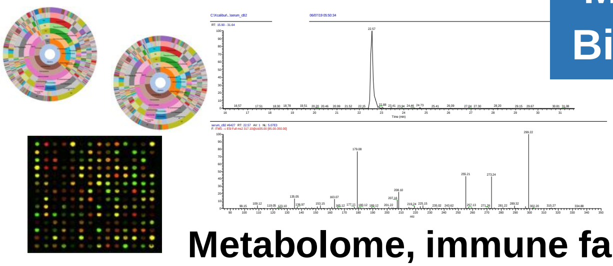
Unification of terms and concepts

Immunity
Lifestyle
Physiological
⋮

Database

MANTA interface

Metabolites and Biological factors



Metabolome, immune factors, etc.

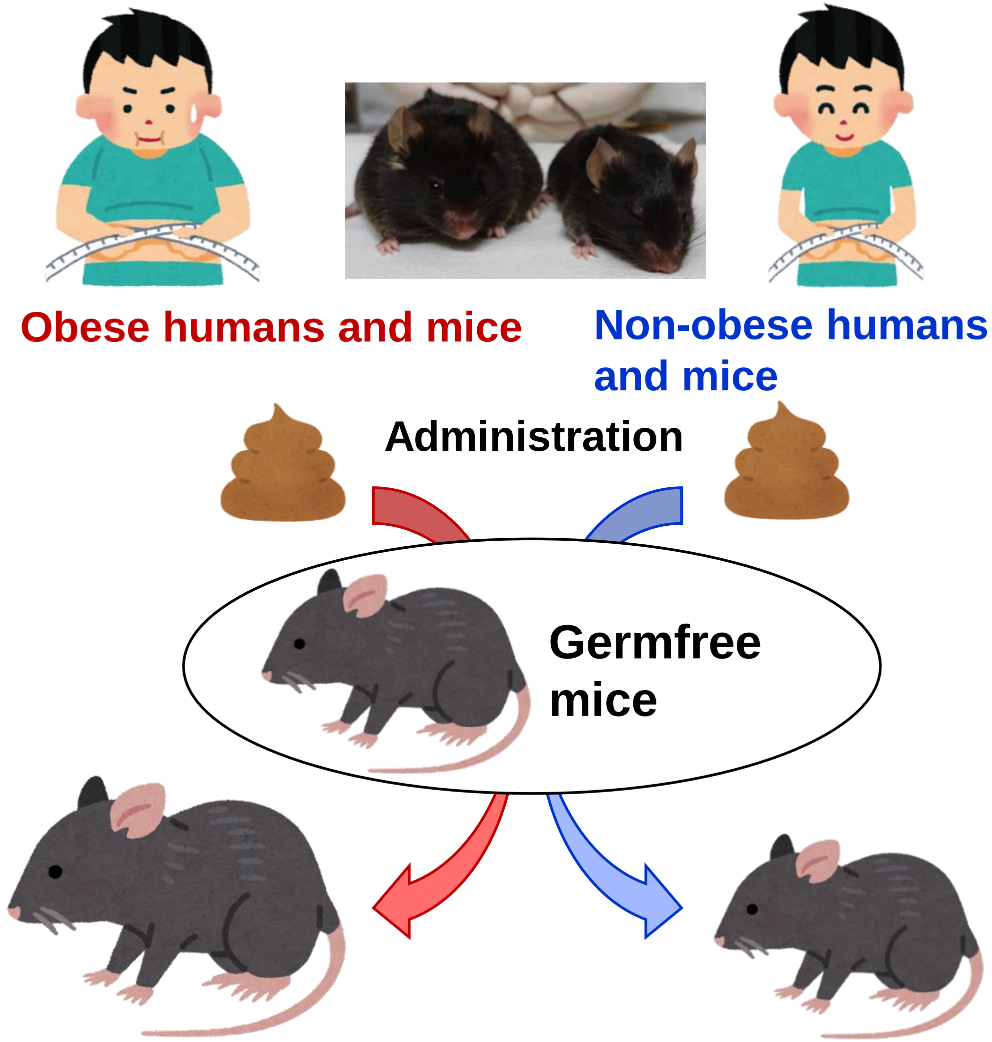
Integrated analysis platform

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

Chen YA et al, PLoS ONE (2020)

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

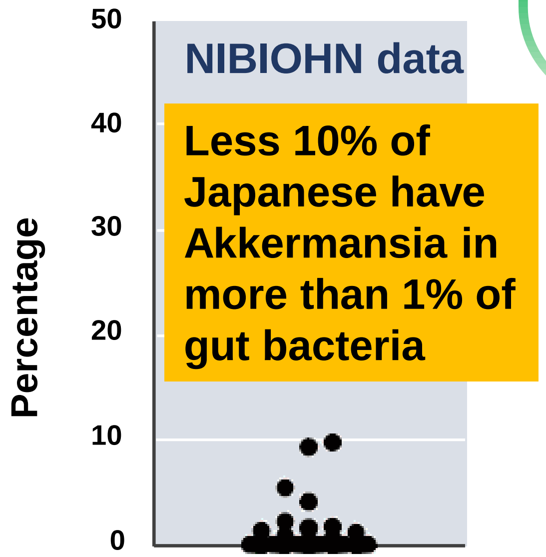
› EFSA J. 2021 Sep 1;19(9):e06780. doi: 10.2903/j.efsa.2021.6780. eCollection 2021 Sep.

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

nutrition insight

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

Japanese



Less 10% of Japanese have Akkermansia in more than 1% of gut bacteria

Ave 0.4±1.49

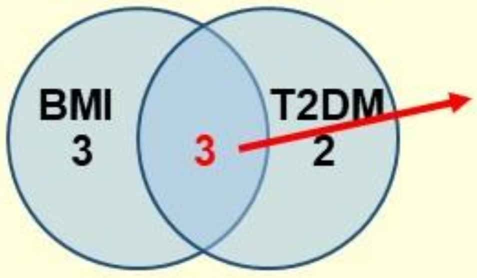
***Akkermansia muciniphila* is rare in Japanese**

↓

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

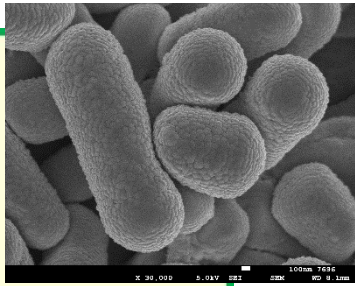
Blautia wexlerae **is abundant in non-obese (left) or non-diabetic (right) individuals**

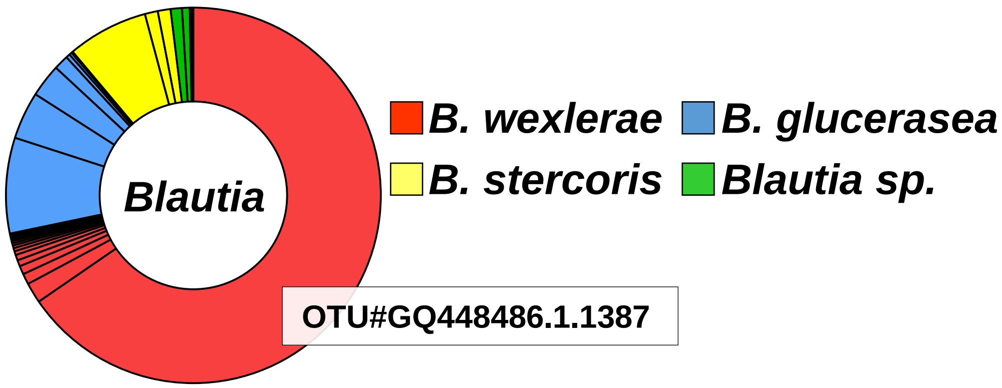


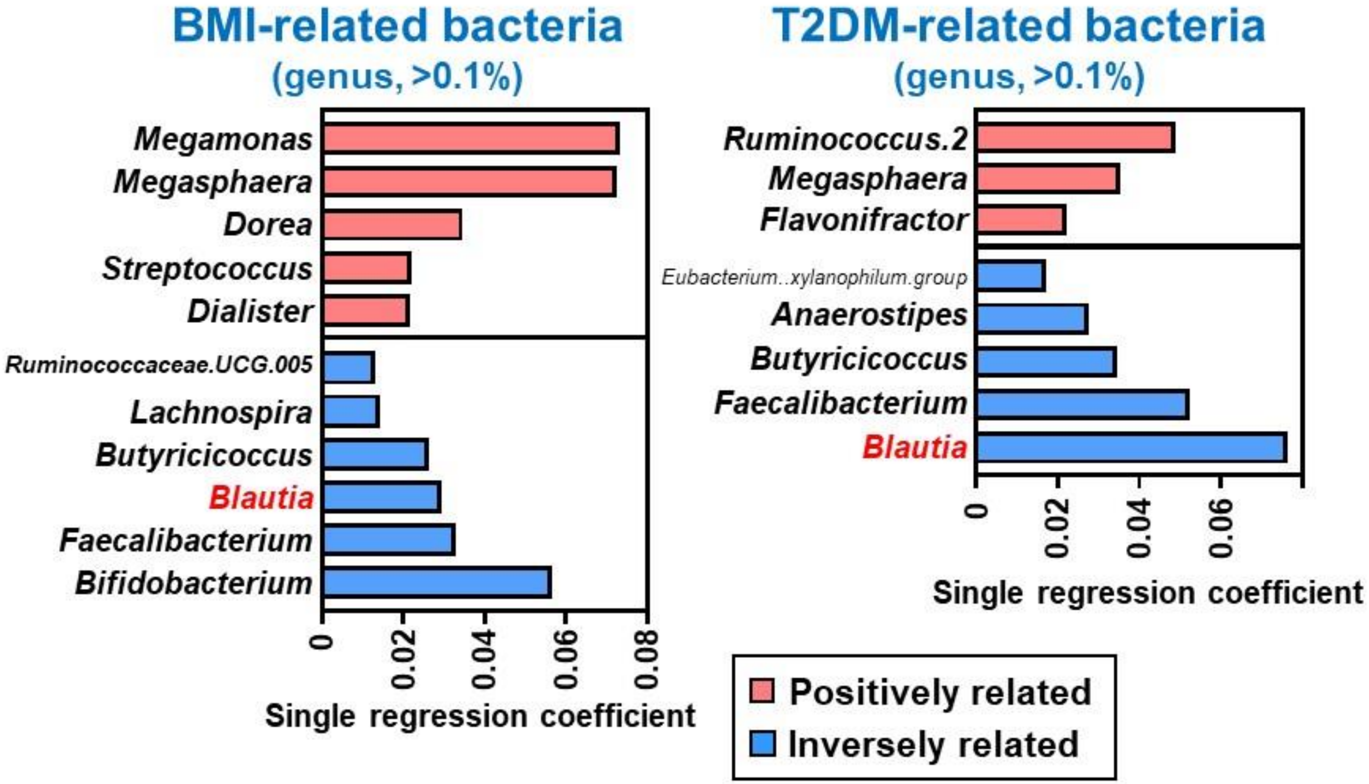
Blautia

Butyricicoccus

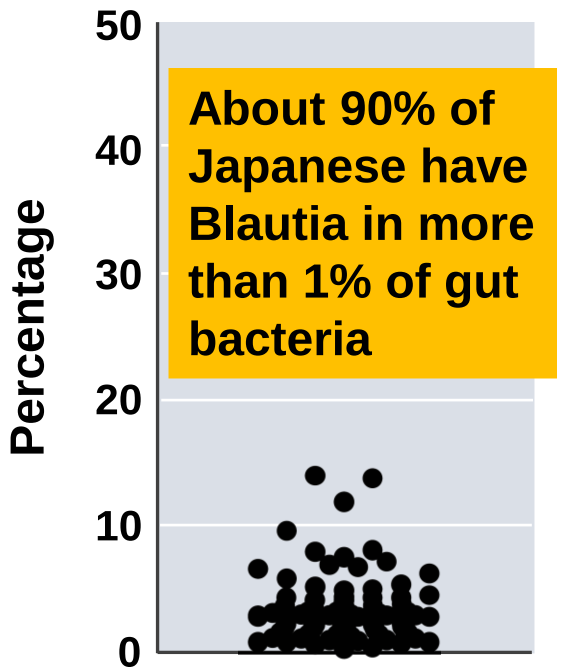
Faecalibacterium







NIBIOHN data

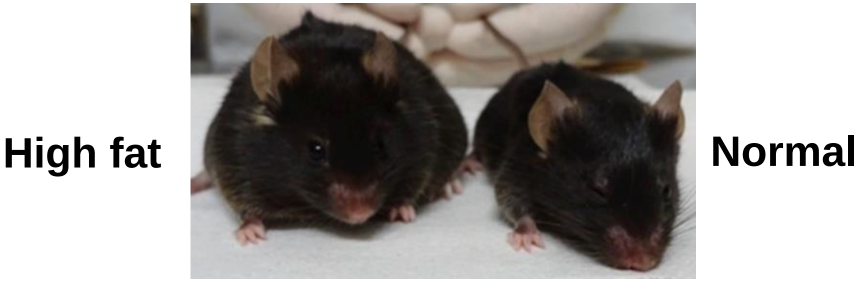


About 90% of Japanese have Blautia in more than 1% of gut bacteria

Ave 3.31±2.46

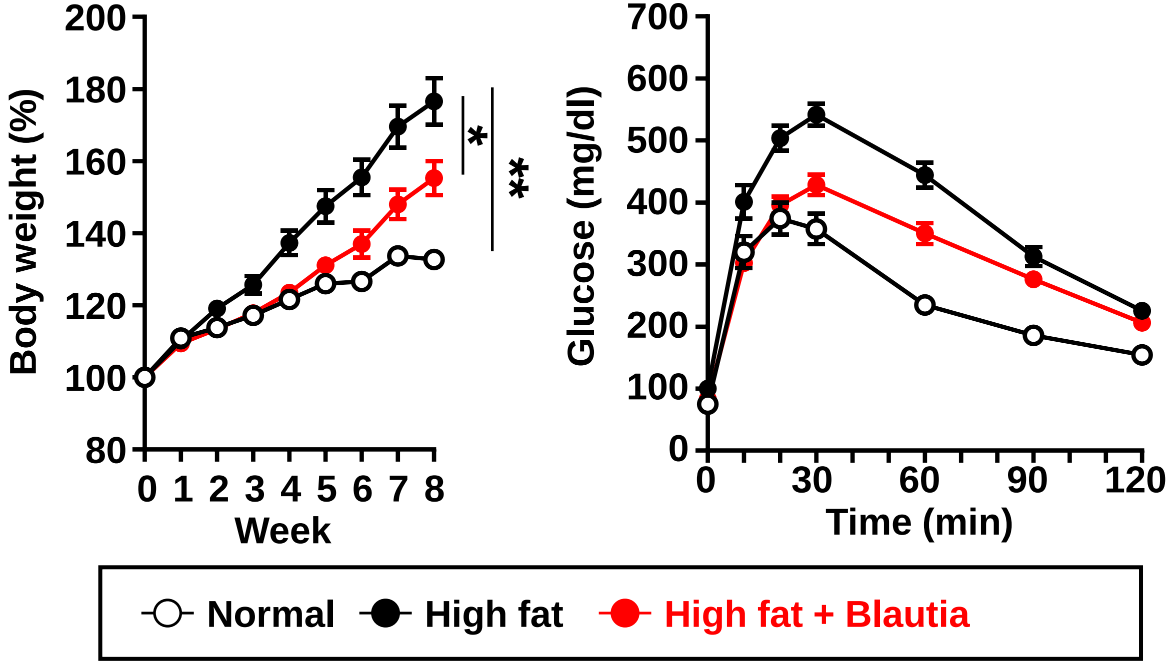
Hosomi K et al, Nat Commun (2022)

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



Body weight

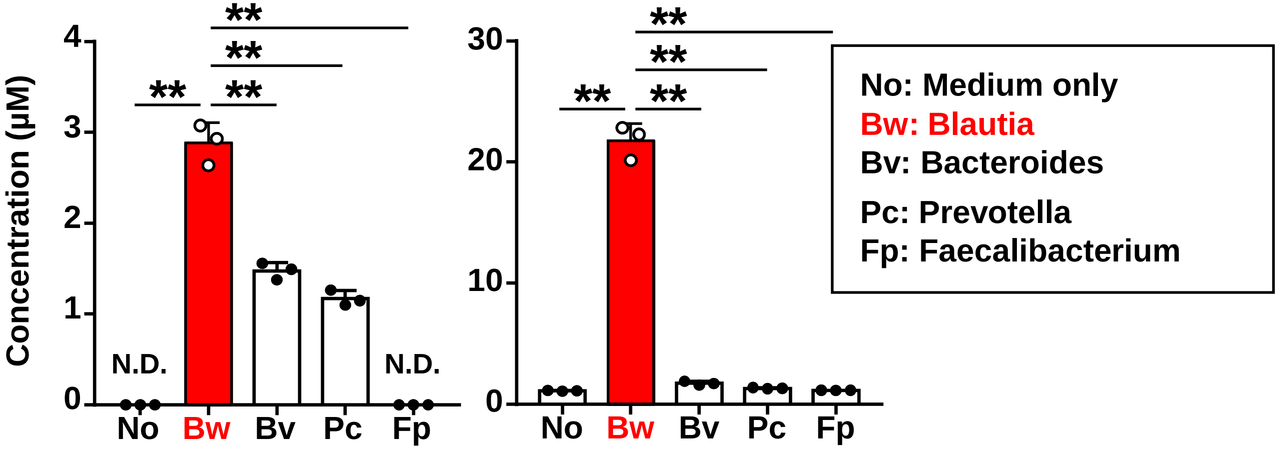
Diabetes



Metabolomic Analysis

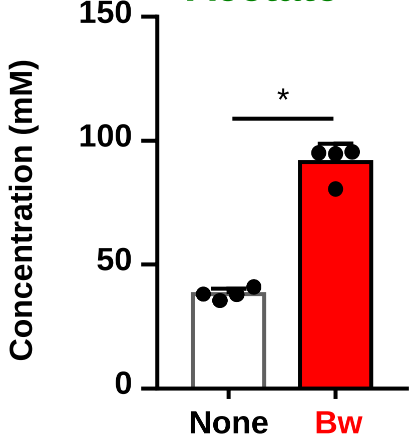
S-adenosylmethionine

L-ornithine



SCFA

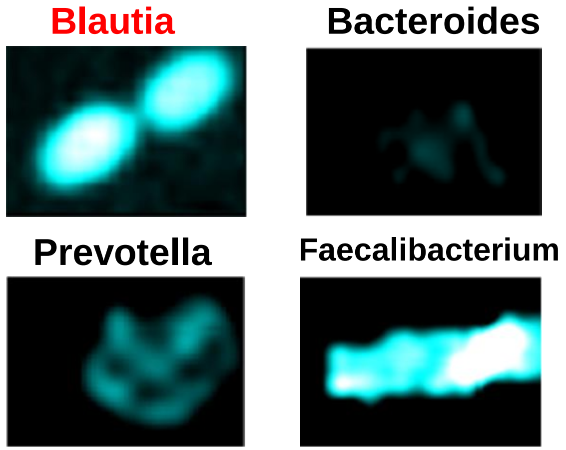
Acetate



Raman analysis

Takeyama's group (Waseda U)

Amylopectin



Hosomi K et al, Nat Commun (2022)

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

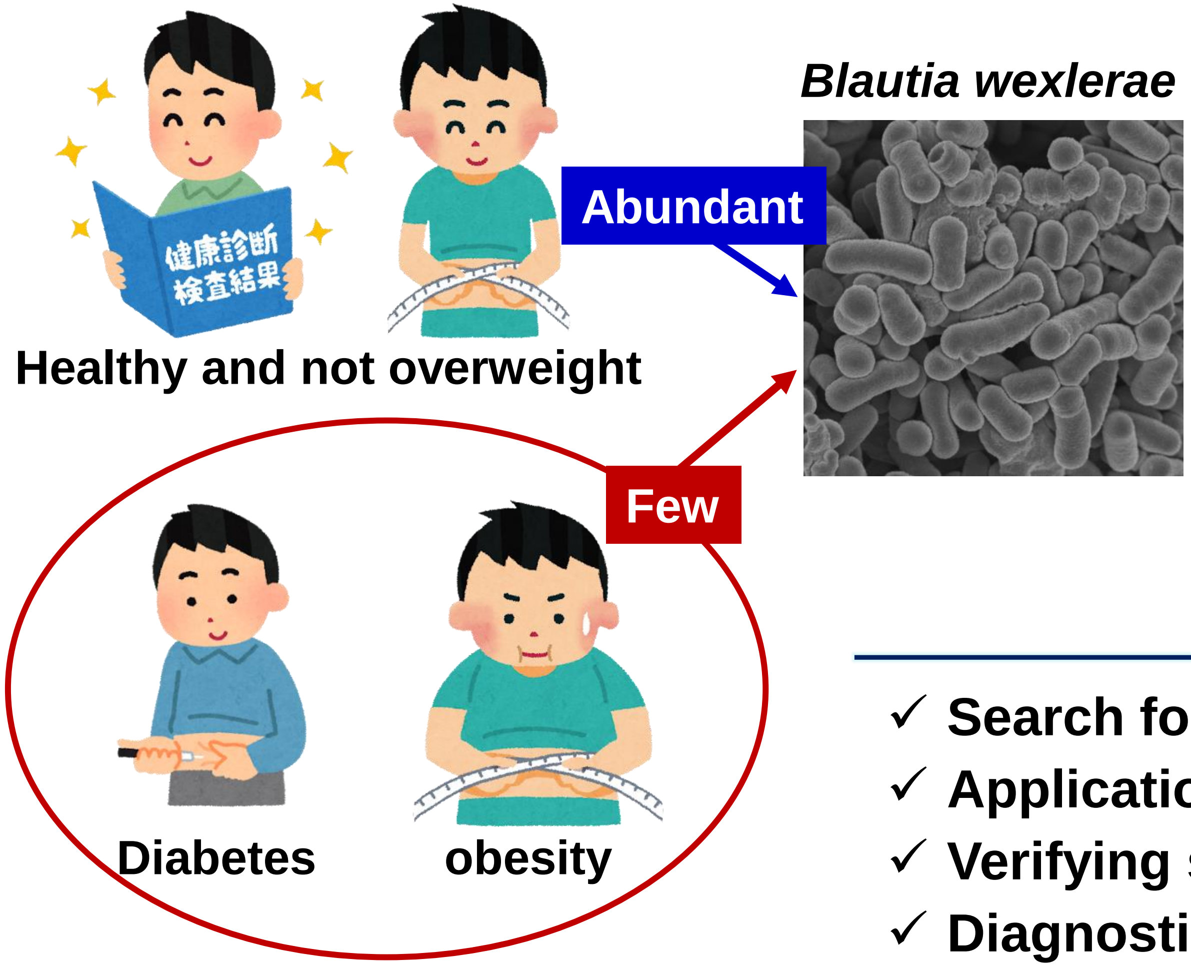
nature communications

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



Healthy and not overweight

Abundant

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】

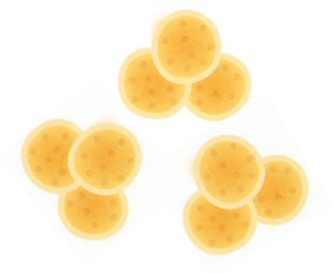
Improvement of the gut environment (e.g. increase in short-chain fatty acids)

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

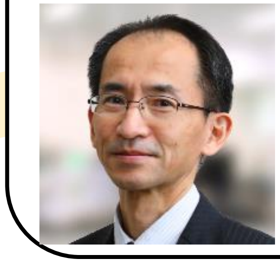
Co-PI (The Univ of Osaka)

Hiroyuki Mizuguchi

iPS- or Organoid-based Epithelial Cell Function

Co-PI (The Univ of Osaka)

Masuo Kondoh



Pharmaco-microbiomics Analysis