Microbiome/biomarker analysis involved in dementia

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Original measure: Construction of a database of gut microbiota in healthy Japanese people to contribute to establishment of new prevention methods for lifestyle-related diseases (MHLW)

Issues and Goal

Social conditions and the significance of this measure

By converting the data on lifestyle and health in Japan and the data related to health and medical care that have been dispersed or unused into big data, we develop the healthcare market through elucidation and development of healthy foods and custom-made provision of them. Then, we need to be the first in the world to realize a social system that implements health care through food consumption, specifically by self-care, early detection, and early intervention in the health and pre-disease (Mibyo) stage. In addition, dementia, which is increasing worldwide, is a disease that hinders extension of healthy life expectancy, and preventive measures are strongly required. Japan has one of the world's highest rates of dementia in its population, with Alzheimer's disease accounting for half of the cases.
In the original measure, we established a healthy person database (containing metabolome, genes, exercise, physical functions, diet/nutrition information, etc.) that can collate with the gut microbiota database of patients in Japan. As of the end of 2018, we established a healthy person microbiome database containing abundant metadata such as lifestyle on a scale of 1,200 people, and we will expand the data to 5,000 people. For the reasons above, we will further collect data that contributes to prevention of dementia in this measure.

Social vision to aim for
A society where medical care and healthcare are linked and people can participate in society for a long time

<Market sector>
Life improvement healthcare, functional food, and digital health

Development of foods and beverages that contribute to maintenance and promotion of health in countries where the health insurance system is developing
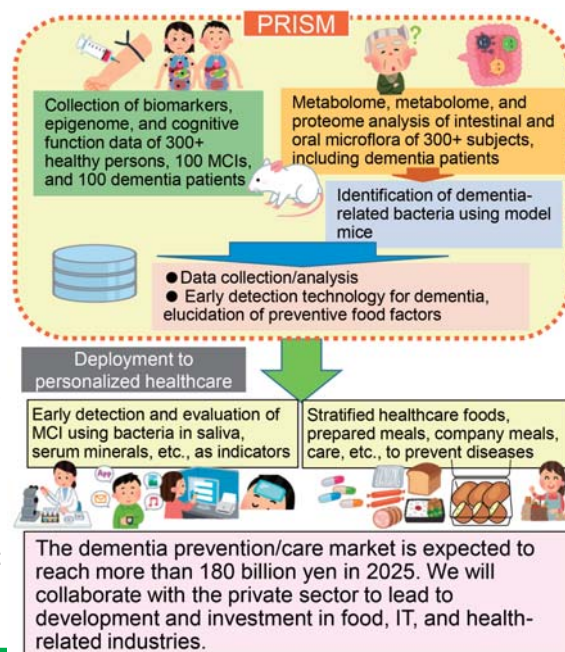
Health promotion-related industries by improving lifestyles such as food, exercise, and sleep · Digital medical care (diagnosis/treatment) · Development of non-invasive/minimally invasive testing equipment

Overview

Biomarker analysis related to dementia, analysis of oral microflora

As development of technologies for early detection and evaluation of dementia and development of dementia-preventive foods were not definitive, extension of healthy life expectancy was hindered. Therefore, we will collect and analyze data on biomarkers (blood constituents, 80 cytokines, amyloid-β, etc.), epigenome, gut microbiome, cognitive functions, etc., of more than 500 healthy persons (including patients with mild cognitive impairment (MCI) and dementia). Then, by integrating the subject data for two years, we will search for mental and physical conditions and lifestyles related to aging and cognitive functions. Furthermore, we will search for biomarkers associated with cognitive functions by comparing data from dementia patients.
In addition, by metagenomic, metabolomic, and proteomic analyses of the oral microflora of approximately 300 subjects, including dementia patients, we will identify the microbiome specifically associated with the disease. Also, gnotobiotic animals produced by colonizing the intestinal flora (feces) of elderly subjects including dementia patients in sterile mice or the pathology specific to dementia patients using AD model mice (neurogenesis/degeneration, amyloid deposition, etc.), or intestinal microbiota related to behavioral/cognitive abnormalities are identified. Thereby, their molecular mechanisms will be elucidated. Through these efforts, we will develop technologies, products, and services for early detection of onset of mild cognitive impairment or dementia and highly accurate assessment of its severity to accelerate public and private R&D of foods, healthcare, and intervention methods that contribute to maintenance of cognitive functions.
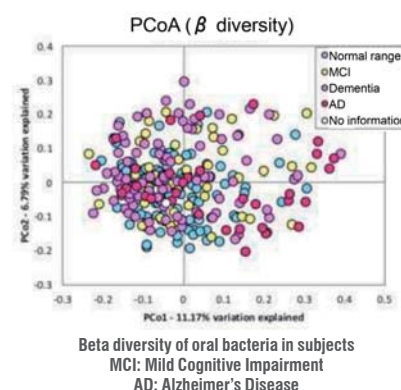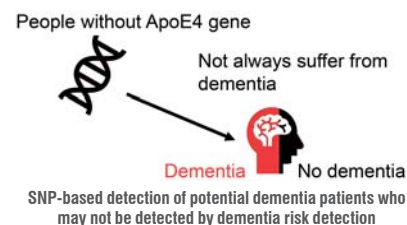

PRISM
Collection of biomarkers, epigenome, and cognitive function data of 300+ healthy persons, 100 MCIs, and 100 dementia patients

Metabolome, metabolome, and proteome analysis of intestinal and oral microflora of 300+ subjects, including dementia patients

Identification of dementia-related bacteria using model mice

● Data collection/analysis
● Early detection technology for dementia, elucidation of preventive food factors

Deployment to personalized healthcare

Early detection and evaluation of MCI using bacteria in saliva, serum minerals, etc., as indicators

Stratified healthcare foods, prepared meals, company meals, care, etc., to prevent diseases

The dementia prevention/care market is expected to reach more than 180 billion yen in 2025. We will collaborate with the private sector to lead to development and investment in food, IT, and health-related industries.

Achievements to date and expected positive ripple effects

Markers for early detection of dementia and bacteria in saliva

Based on the data of more than 500 subjects, we clarified factors related to cognitive functions such as blood magnesium, cholinesterase and the risk genes in subjects who do not have gene ApoE4, which is considered to be related to dementia, and applied for a patent. In addition, we identified 50 bacterial species in saliva related to dementia (especially four bacterial species strongly associated with dementia), and we constructed a microbiome/biomarker analysis prediction model involved in dementia by machine learning. In FY2021, we will increase the number of subjects with mild cognitive impairment and dementia, verify detection of the risk of developing dementia by the markers we found, and establish a method for early detection of dementia using a set of salivary bacteria markers with higher prediction accuracy than before using machine learning.

Exit strategy: inducing private R&D investment

This measure will contribute to development of technology for early detection and evaluation of dementia, a major factor preventing extension of healthy life expectancy, and to acceleration of research on development of foods that contribute to maintenance of cognitive functions. The achievements of the development will be made into intellectual property, and then along with PRISM implementation they will be actively transferred to private companies that provide services for early detection of dementia, development of functional foods that contribute to maintenance of cognitive functions, and new care services, to accelerate social implementation. As an effect of inducing private investment, early diagnosis methods for dementia, dementia prevention food and care services, etc., will be developed, leading to development and investment of industries in the market of MCI and dementia early detection, care support service, and healthcare food (projected to be 61.1 billion yen in FY2020, market expansion of more than three times in five years) ⇒ Thus, the healthcare industry will increase to be 100 billion yen per year.
The amount contributed by the private sector was about 344.82 million yen in FY2020 (125 million yen in the initial plan).

People without ApoE4 gene
Not always suffer from dementia
Dementia No dementia

SNP-based detection of potential dementia patients who may not be detected by dementia risk detection

PCoA (β diversity)

○Normal range
○MCI
○Dementia
▲AD
○No information

PCo2 · 6.77% variation explained
PCo1 · 11.17% variation explained

Beta diversity of oral bacteria in subjects
MCI: Mild Cognitive Impairment
AD: Alzheimer's Disease

Promotion of large-scale building using wood
Research and development (R&D) project for implementation of large-scale timber construction contributing to expand wood demand

Program Director **MIDORIKAWA Mitsumasa** Professor emeritus at Hokkaido University (President, Building Research Institute, National Research and Development Agency)

Original measure: R&D on technology for mid- and high-rise buildings and other of timber construction (Building Research Institute)/Development of design and construction technology for mixed-structure buildings using new wood materials (National Institute for Land and Infrastructure Management: NILIM)

Issues and Goal

Issues
To expand the demand of timber, the revised Building Standard Law (effective June 2019) has rationalized the regulations on the performance and others required for mid- and high-rise buildings using wood, but the lack of the technical data on designing and evaluation methods to facilitate construction disturbs their wide use.

Goal
For large-scale timber constructions contributing to expand the wood demand, we will gradually provide the technical evidence of the regulations and the generalized and usable experimental design documents.

Overview

Overview of the theme
This measure is a part of "R&D/Human Resources" (Bio-Strategy 4.6) among the efforts promoted by the "Large Timber Utilization/Smart Forestry Working Team (WT)" established under the Bio-strategy task force. It expands and develops the various projects in the original measures below: development of evaluation technology for structural elements, members, joints, etc., of medium-high-rise timber buildings, examination of floor impact sound insulation performance, and development of design case prototypes for medium-large-structure mixed structure buildings using wood materials utilizing CLT (Cross Laminated Timber). Hence, through the R&D to prepare and standardize designing technics for all-purpose examples, we will accelerate proliferation of our results in the market.

(1) Development of high-rise timber building designing all-purpose technology to increase wood demand

Specific initiatives
We will carry out the R&D (1) to (3) below:
(1) Development of designing for all-purpose technology for high-rise timber buildings to increase wood demand
  1.1 Development of design technology for general-purpose high-rise laminated timber structures
    Development of technology for high-rise timber buildings with laminated timber structures that are useful for securing larger timber demand and more space.
  1.2 Development of technology for high-rise timber buildings that contribute to effective use of land
    Development of technology for high-rise timber buildings using the mass timber construction that can be applied to effective use of land in times of disaster and to early development of disaster reconstruction houses.
(2) Development of technology for spread of mid- and high-rise buildings using mixed-structure buildings using wood materials
  2.1 Development of technology for promoting large-structure buildings that have wooden structural materials on the surface, which contributes to cost reduction
    Development of technology for large-structure timber buildings without fire protection, which is now permitted due to amendment of the Building Standard Law
  2.2 Development of technology for faster construction of mid- and high-rise buildings utilizing mixed-structure buildings using wood materials
    Development of technology for buildings utilizing mixed-structure buildings using wood materials that can be applied to early development of disaster reconstruction houses in times of disaster
(3) Development of technology for improving the comfort from the viewpoint of the acoustic environment of timber buildings
  - Added an example of floor cross-section specifications for the CLT panel construction method to the standard for evaluating acoustic environment performance (notice) based on laws and regulations.
  - Develop and publish examples of cross-sectional specifications for securing acoustic environment performance

(2) Development of technology for proliferation of mid- and high-rise buildings using mixed-structure buildings using wood materials

(3) Development of technology for improving the comfort from the viewpoint of the acoustic environment of timber buildings
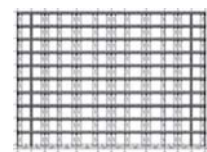
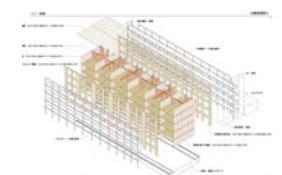## Achievements to date and expected positive ripple effects

R&D achievements
(1) Development of designing all-purpose technology for high-rise timber buildings to increase wood demand
  - Case study of high-rise timber buildings overseas
  - Test on a part of structures of high-rise timber buildings and examination of designing methods
  - Listing of datum of structural elements
  - Designing case study under allowable unit stress on mass timber construction and others within elasticity
  - Clearing condition for higher quality of post-installed anchors
(2) Development of technology for spread of mid- and high-rise buildings utilizing mixed-structure buildings using wood materials
  - To show the structural material of timber on the surface, development of rational structures of mixed-structure buildings using wood materials and design techniques for fire safety
  - To show the structural material of timber on the surface, expansion of structures and fireproof data through experiments of required walls, floors, joints, etc.
(3) Development of technology for improving the comfort from the viewpoint of acoustic environment
  - Collection of cross-section specifications and measurement examples of timber buildings
  - Survey of acoustic environment performance for actual buildings, and listing floor impact sound insulation performance for each floor cross-section specification

(1) Example of structural design for a 10-story disaster reconstruction house applying mass timber construction

(2) Medium-rise disaster reconstruction houses of mixed-structure buildings using wood materials

Exit strategy
When the achievements of this measure are reflected in official guidelines in the related field, they will become common knowledge for both designers and building confirmation judge sides. It will improve compliance with structural and fire safety standards, enhance the efficiency of design and inspection involving advanced and complex simulations, and accelerate spread of large-structure buildings using timber.

(3) Measurement taken at the Tsukuba CLT experimental building