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Health and Nutrition (NIBIOHN)

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The Institute's social media accounts

The official YouTube channel

The official X (formerly Twitter) account

The official Instagram account

2024.00

NIBIOHN

NIBIOHN 2024

A research institute committed to people's health

National Institutes of
Biomedical Innovation,
Health and Nutrition

A research institute committed to people’s health

Living long with healthy conditions has always been a long-standing desire of humankind. For people suffering from illness and their families, living in darkness without hope of a cure or living with even the slightest hope of a cure makes a huge difference on their life.

In order to be a beacon of hope for such people, we are taking on the challenge of interdisciplinary research in both the medical and health sciences for drug discovery that leads to new treatment possibilities and researches on nutrition and physical activity that leads to prevent illness. Always with a spirit of challenges, we are deeply committed to revolutionize Japan and the world from Osaka.

As a research institute committed to people’s health, we will not conduct research simply for the sake of research, but rather always aim for new technological innovations, promoting collaborations with medical institutions, private companies, and local and central governments, and conduct research that truly benefits people and society.

In addition to collaboration between industry, government, and academia, we also work together with patients to accelerate research that will give back to society.

President, Yusuke Nakamura

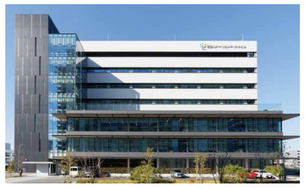
Since the National Institute of Biomedical Innovation (NIBIO) and the National Institute of Health and Nutrition (NIHN) merged in 2015 to form the National Institutes of Biomedical Innovation, Health, and Nutrition (NIBIOHN), a six-center system, which includes the Center for Drug Design Research, has been established based on the first med- to long-term plan. NIHN had been located in Tokyo, but was relocated to Kita Osaka Health and Medical Care City (“KENTO”) in Osaka Prefecture, and both institutes will deepen collaboration with medical institutions and patients to develop a project to extend healthy life expectancy.
In 2024, the post-war baby boomer generation has reached the advanced age group, raising the importance of living a long life with the healthy condition. Amid this, our second 7-years med- to long-term plan started in 2022. The plan addresses various issues with an “era of 100-year lifespans”. One of the keywords is "individual optimization." In the future, it will be necessary to provide optimal guidance and medical care tailored to each individual, whether it is to maintain and improve health through diet and exercise or to select treatment methods in the disease condition. We would like to further advance drug discovery and nutrition research using cutting-edge AI technology, and contribute to our society.
Based on extensive collaboration with two Osaka Prefectural Hospitals, the Osaka International Cancer Institute and the Osaka Women’s and Children’s Hospital, NIBIOHN has begun working with patients, medical institutions, and research institutes to make incurable disease to be curable. It is difficult for private companies to develop drugs for intractable diseases and rare diseases. Fulfilling its purpose as a national research facility under the three key words of medical infrastructure, health and nutrition, NIBIOHN has made research and development targeting these diseases as one of our priorities.
Additionally, in order to take full advantage of the benefits of integrating the two research institutes, from health maintenance to drug development, we will further focus on areas that integrate the pharmaceutical and health/nutrition fields. We are exploring new possibilities, such as in our research on nutrition, intestinal bacteria, and immunity.
We will continue to make further efforts to contribute to extending healthy longevity through the fundamental technologies for the development of innovative medicines, research on food, nutrition, and exercise, and basic research. We would like to ask for your continued support as we move forward.

Contents

Promoting local open innovation and interdisciplinary activities leveraging a network of research infrastructures

In 2022, the National Institute of Health and Nutrition (NIHN) is moving to the Northern Osaka Health and Biomedical Innovation Town (NohBIT or “*Kento*” in Japanese), which extends over parts of Suita and Settsu, Osaka Prefecture. The relocated institute aims to promote open innovation in partnership with the National Cerebral and Cardiovascular Center, Suita Municipal Hospital, private enterprises, and other organizations in the area. In collaboration with local communities, the NIHN will find ways to apply research findings to local settings. Moreover, the relocation of the NIHN will strengthen its ties with the National Institute of Biomedical Innovation (NIBIO) located in the International Cultural Park (“*Saito*” in Japanese), thereby expanding interdisciplinary research collaboration.

National Institute of Biomedical Innovation (NIBIO),
International Cultural Park (*Saito*, Ibaraki City, Osaka)



National Institute of Health and Nutrition (NIHN),
Northern Osaka Health and Biomedical Innovation Town (*Kento*, Suita and Settsu, Osaka)

History

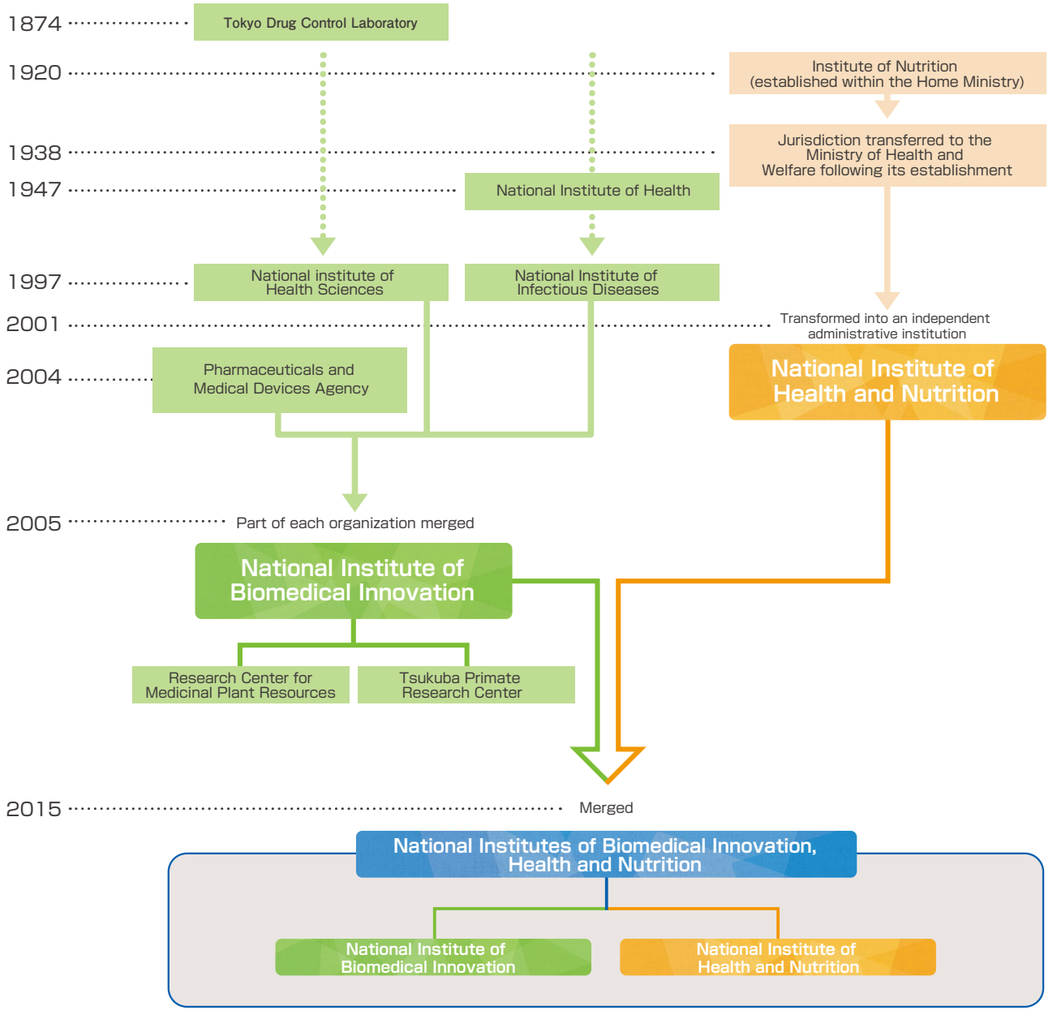
The National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN) was founded on April 1, 2015, by integrating the National Institute of Biomedical Innovation (NIBIO) with the National Institute of Health and Nutrition (NIHN).
The establishment of NIBIOHN was a part of the effort to review independent administrative institutions under the *Basic Policy regarding the Reform of Independent Administrative Institutions*, approved by the Japanese Cabinet in 2013, for the purpose of promoting comprehensive research by integrating expertise in drugs, food, and other related fields.

Quick History of the National Institute of Biomedical Innovation (NIBIO)

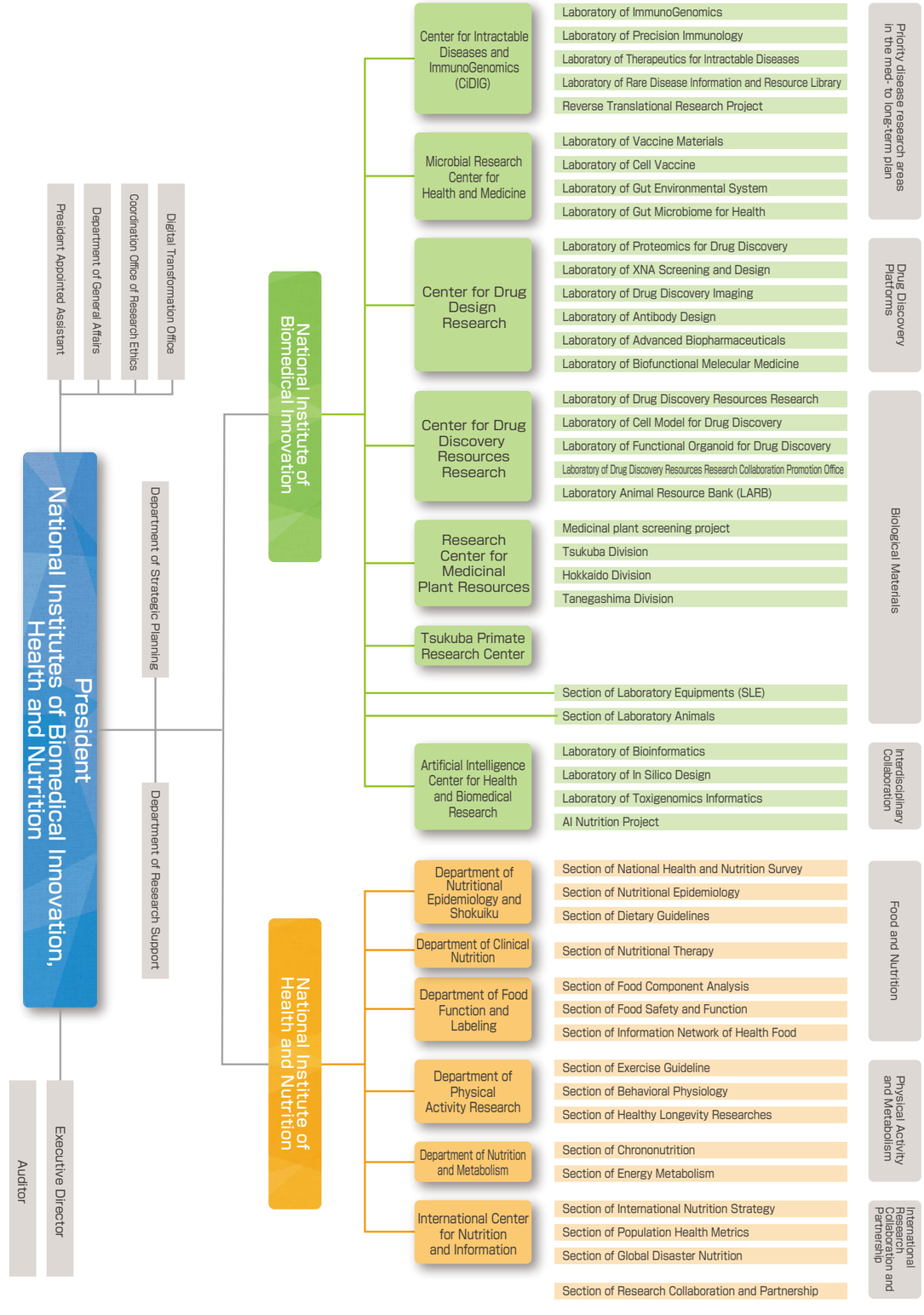
NIBIO was established in 2005, with the Osaka branch of the National Institute of Health Sciences as the nucleus, and by integrating parts of the National Institute of Infectious Diseases and the Pharmaceuticals and Medical Devices Agency.
NIBIO's mission is to build the foundation for improvement of pharmaceutical and other related technologies by conducting universal research that contributes to the development of drugs and other products, as well as biological resources, and by promoting research and development in the private sector or other settings for the overall purpose of improving the health of the people of Japan.

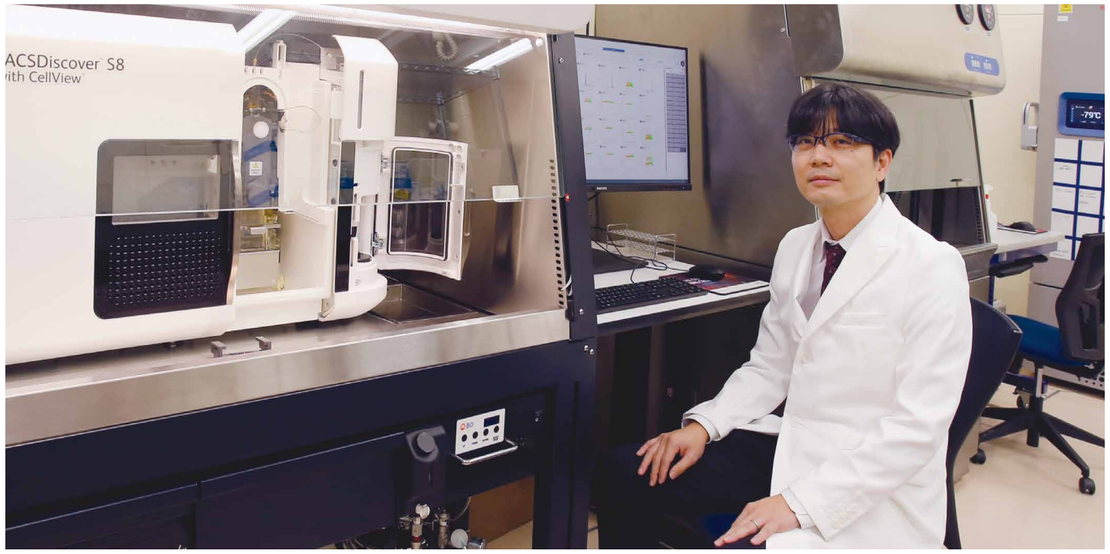
Quick History of the National Institute of Health and Nutrition (NIHN)

NIHN can be traced back to the Institute of Nutrition established in the Home Ministry in 1920. After the Ministry of Health and Welfare was founded in 1938, oversight of NIHN was transferred from the Home Ministry to the Ministry of Health and Welfare, and the NIHN was transformed into an independent administrative institution in 2001.
NIHN's mission is to conduct surveys and studies regarding the maintenance and promotion of health of the people of Japan, as well as surveys and studies regarding nutrition and diet for the purpose of improving and advancing public health.



Organizational Chart





Center for Intractable Diseases and ImmunoGenomics (CiDIG)
Center Director, **Takuya Yamamoto**

A professional's commitment to research

I have always focused on human immunology research ever since I was a student. Before my posting at NIBIOHN, I had the opportunity to study at the forefront of translational research at major infectious disease research institutes in Japan, France, and the United States. However, I felt that someday I would like to take part in drug discovery and vaccine development research originating in Japan. After being approached by NIBIOHN, which is one of the most active translational research centers in Japan, I decided to return to Japan.

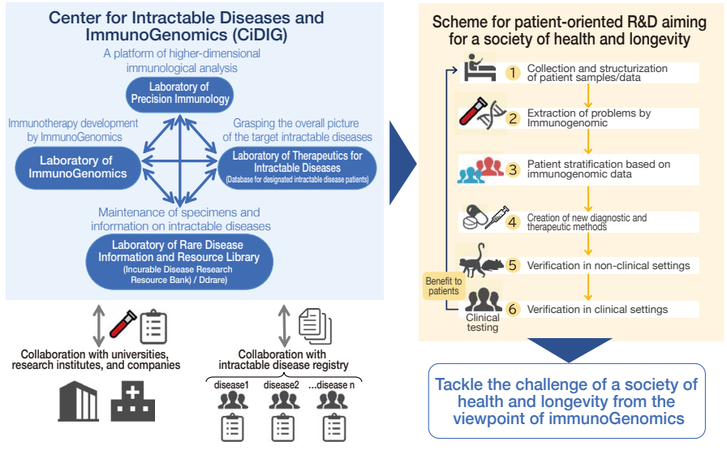
Informing patients in a timely manner and contributing broadly to people's health and longevity through interdisciplinary research involving experts in the fields of intractable disease, genome and immunology

Exploring approaches to intractable diseases, cancer and infectious diseases by elucidating the hidden connections between genomic and immune information

With the development of computer science, a paradigm shift to research and development utilizing big data has long occurred in the field of life sciences. With that being said, social implementation schemes that aim to return the benefits to patients are still underway. To achieve this, it is important to comprehensively prepare and analyze all human phenotypes as general-purpose data, and to conduct omics analysis that attempts to elucidate genomics, transcriptomics, proteomics, and metabolomics. The phenotype of the human genome, known as the blueprint of the human body, varies depending on age, gender, health condition, and disease. Therefore, it is necessary to examine biological samples as temporally and spatially linked data in high resolution, and a high level of expertise is required for such analysis.

In order to make the most of valuable biological samples to benefit patients, it is necessary to collect and structure high-quality biological samples that serve as the source of data and clinical data linked to each sample and to appropriately implement the series of processes based on established expertise, from the digitization of samples through experiments to advanced data analysis. Against this backdrop, the Center was established in April 2023 to promote research and development from the perspective of collecting clinical information as well as combining genomic and immune information, to develop and implement diagnostic, preventative, and therapeutic methods for intractable diseases, cancers, and infectious diseases.

Figure.1



Utilizing platforms for high-dimensional immunological analysis seamlessly connecting clinical and non-clinical data

The Laboratory of Precision Immunology promotes patient-centered, -oriented, -focused drug discovery research for intractable diseases, cancer, and infectious diseases, based on realizing "precision medicine" that delivers optimized medical care to each patient through an immunological approach. This requires an understanding of the complexities of the human immune system, which differs from individual to individual, and to deepen our understanding of diseases by identifying problems in individuals or specific disease groups. For this reason, our laboratory has equipped an analysis platform (advanced immunological analysis platform) that can analyze the differences in the immune system and response to immunogens in each individual from multiple perspectives and with high resolution (Figure.1).

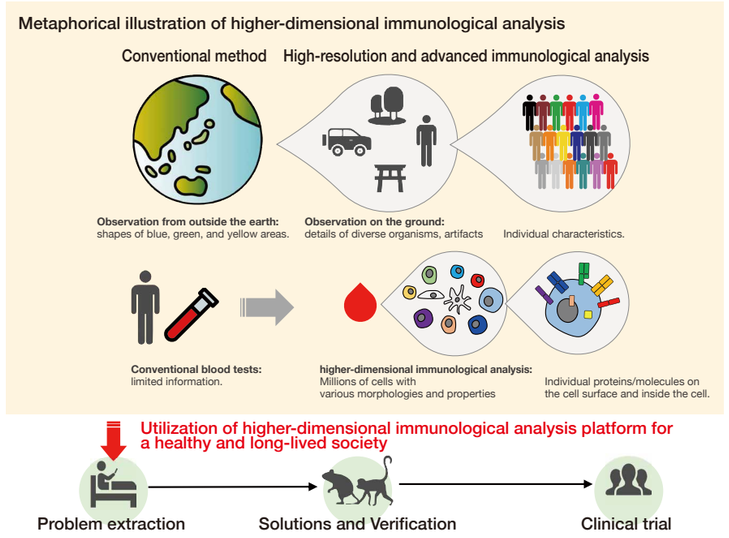
By making full use of this platform, we aim to elucidate immune responses that exhibit various phenotypes for each disease and patient, search for new biomarkers and surrogate markers, and develop new diagnostic methods, immunotherapy, and preventive and therapeutic vaccines. This analysis platform is used for research on immunotherapy for chronic persistent infectious diseases such as pancreatic cancer, HTLV-1 infection, AIDS, and hepatitis B, as well as for non-clinical and clinical trials in vaccine development for acute infectious diseases such as influenza and novel coronavirus infections.

Developing cancer immunotherapies based on genomic information

The Laboratory of Immunogenomics conducts genomic analysis of various diseases, and in the case of cancer, we are working on the development of personalized treatments, especially immunotherapy, based on genomic information. Over the last decade, the importance of immunity in cancer has been reported, and it has been found that cancer-specific antigens, neoantigens, small fragments of mutant proteins coded by somatic genomic mutations in cancer cells are important targets for the immune system, mainly by T cells. In other words, if we can identify a neoantigen(s) that is recognized by T cells, we can attack the cancer by activating patient's immune responses. However, neoantigens vary among individual cancer patients, so it is necessary to identify the "right" targetable neoantigens for each cancer patient. We have developed a system to efficiently predict neoantigens based on information on genomic mutations identified through the comprehensive genome sequencing and bioinformatic technology.

Using this system t, we showed that T cells specific to the predicted neoantigens were successfully induced using blood samples from patients and healthy donors. We are currently conducting clinical research on cancer vaccines targeting personalized neoantigens, which is expected to provide new treatment options for patients who have no treatment option. We are developing new cancer immunotherapies targeting cancer cells expressing neoantigens, such as T cell therapies using genetically modified T cells expressing with T cell receptors or antibodies specific to neoantigens.

Figure.2



What are intractable diseases? Why should we find a cure?

Generally, intractable diseases are diseases that are difficult to cure or for which no cure has been found. In 2015, the Ministry of Health, Labour and Welfare (MHLW) defined 110 designated intractable diseases that are eligible for medical expense subsidies under the Intractable Diseases Act. Since all of these diseases are rare and research and development is difficult, Japan has put in place a system to support research as a national policy. The Laboratory of Therapeutics for Intractable Diseases and the Laboratory of Rare Disease Information and Resource Library are working to develop research resources that will serve as the foundation for research on intractable diseases.

＊The National Database of Designated Intractable Diseases of Japan

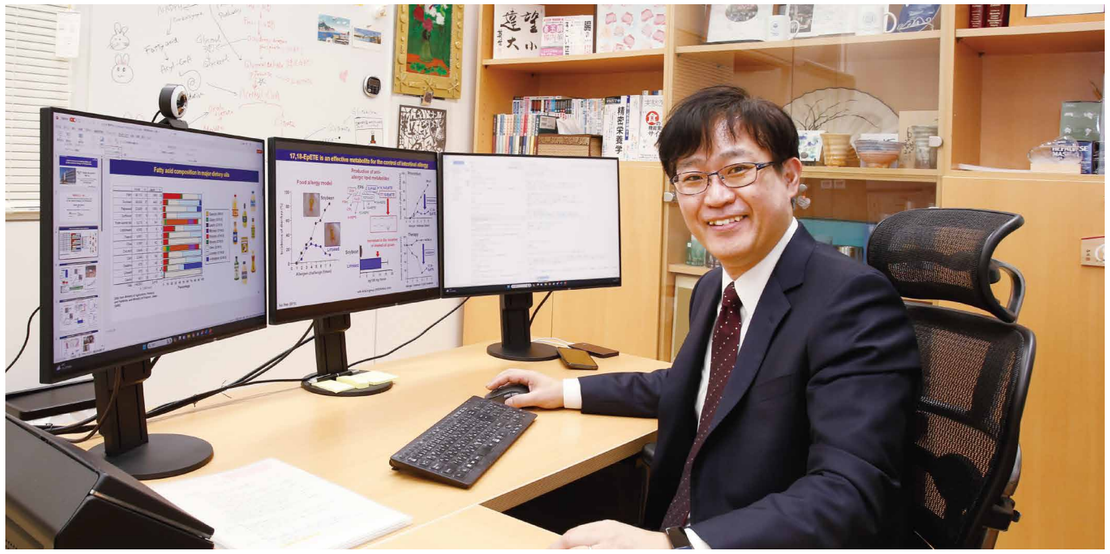
Since 2015, the number of targeted diseases has expanded, and currently 338 diseases are defined as designated intractable diseases. The total number of recipients is about one million, and the clinical research forms prepared and submitted when applying for medical expense subsidies are used to promote research on intractable diseases with the consent of the patients. For this purpose, we have been entrusted by MHLW to operate the National Database of Designated Intractable Diseases of Japan (registration and provision of data) as a disease registration center operator.

＊Resource and database for intractable disease research

Patient samples (plasma, DNA, etc.) and information (clinical information, etc.) are important research resources in the development of diagnosis and treatment methods for intractable diseases. In order to bridge the use of these valuable resources for research, we have been operating the Rare Disease Bank since fiscal 2009, and we are collaborating with a total of 50 medical institutions, including the Rare Disease Research Group, which operates patient registries, to serve as a hub for the collection and distribution of resources. In addition, we analyze clinical trial data on intractable diseases in Japan and overseas, and provide what drugs have been developed for which diseases, from a database called DDrare. We also analyze the gene products and biomolecular interactions that drugs interact with in a cross-functional manner across diseases and post them in DDrare. Based on these findings, we are conducting exploratory research on drug repositioning (applying one drug to another disease) candidates.

Collaborating with experts from research on intractable diseases, cancer and infectious diseases to social implementation

It is believed that the use of big data will lead to innovation in all fields. The barriers to achieving this, however, are high. In order to solve various health problems based on actual clinical practice, it is possible to implement solutions in society only after a process that requires a high level of expertise, symbolized by 1) appropriate collection, management, and structuring of target biological samples and clinical information, 2) appropriate non-clinical and clinical trials, and 3) ensuring the quantity and quality of omics data analysis obtained from such research. At the Center, a team with a high level of expertise organically collaborates to tackle diseases such as intractable diseases, cancer, and infectious diseases, and conducts research on a daily basis so that we can contribute to the health and longevity of the people of Japan through the timely return of research results in forms that benefit patients.



Microbial Research Center for Health and Medicine
Center Director, Jun Kunisawa

Why I became a researcher and my future goals

Originally, I had wanted to work for a trading company, but became a researcher after I found myself fascinated by new discovery through scientific research. Currently, I am working diligently to expand my research to create a new and healthier society.

A Near-Future Vision for a Healthy Society from the Perspective of Gut Environment: Individualized and Stratified Dietary Guidance, Development of New Drugs and Functional Foods

Integrating the medical and health sciences

When you hear the term "gut bacteria," you may imagine that it has something to do with bowel movements, but do you know that gut bacteria may also be involved in various aspects of health such as immunity, allergies, and obesity?

With the merger of NIBIO and NIHN in 2015, NIBIOHN was able to integrate both medical (after illness) and health (before illness) sciences. As one way to take this advantage, we established a group with some laboratories to focus on the relationship between intestinal environment and health and medicine.

The primary function of intestine is absorption of dietary components, which become part of our body. Therefore, the contents and quantity of our diet greatly affect our physical condition in various ways, including obesity and brain function. Intestine also contains numerous numbers of immune cells and affect immune-related diseases such as allergies and inflammation. Thus, the crosstalk in the intestine among diet, bacteria and immunity plays a key role in the control of our health and diseases.

Results obtained from research focusing on the intestinal environment will expand the possibilities of the healthcare industry, including precision nutrition that dietary methods tailored to individual needs, personalized and stratified nutritional guidance, drug discovery, and the creation of functional foods.

Informatics analysis of human big data set and elucidation of mechanisms by animal models

Looking at an overview of our research, we first collect sets of human data in collaboration with various regional partners in Japan. Possible correlations among the collected data are determined using the latest informatics methodologies, and the resultant findings are then validated using animal models. The obtained implications are used to guide future human studies. As we repeat this cycle, we advance our research intended to improve health and prevent and alleviate disease in terms of the intestinal environment (Figure.).

＊Research on humans and practical applications in society

In this project, we collect various data related to lifestyle (e.g. diet, exercise [physical activity], sleep, etc.) and health (medications, health checkup data, disease history, etc.) from residents of different regions in Japan. We also collect blood, stool, and saliva samples to determine the profiles of gut and oral bacteria, food metabolites, immune parameters and so on. As of the end of FY2023, we have created a microbiome database containing data on more than 10,000 individuals, making it one of the largest databases in the world.

By analyzing this data, we are examining regional characteristics of gut bacteria. For example, we investigated the gut bacteria of the residents in Shunan City, Yamaguchi Prefecture. Compared with the national average, Shunan City residents had higher percentages of Bacteroides, bacteria preferentially like protein and lipids. A food survey showed that these residents had a lower intake of dietary fiber than the national average. To apply our research findings in practical settings, we provided personalized guidance that took into account the other identified dietary characteristics.

Research has also suggested that increasing the variety of gut bacteria may lower the risk of various diseases. Since the ingredients in the food we consume serve as the source of nutrition for gut bacteria, a well-balanced diet is important for establishing a beneficial gut bacteria community. Our recent studies have shown that consuming barley containing a large amount of dietary fiber increases the variety of gut bacteria.

＊Exploring the relationship between food and biological functions

Dietary fiber is metabolized by multiple species of gut bacteria into short-chain fatty acids, which serve as the source of energy for the cells lining the colon. Furthermore, short-chain fatty acids help regulate immune function, rendering the body less obesity prone.

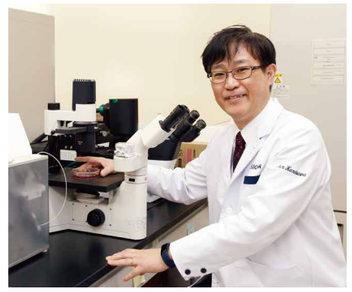
Prompted by these findings, we are conducting cohort studies together with the University of Yamanashi and private sector companies to investigate the health benefits of barley, which contains a large amount of dietary fiber. It is known that there are individual differences in the effects of diet, such as the production of short-chain fatty acids. To reveal the underlying mechanisms creating this individual difference, we have created a machine learning model to predict the health effects of barley and flaxseed together with the NIBIOHN's AI Center for Health and Biomedical Research. By further building on our findings, we hope to create a society where we can propose a diet tailored to individual intestinal environment. We have also developed the Microbiota and Phenotype Correlation Analysis (MANTA) platform, which facilitates the search for factors related to specific health conditions. This platform enables us to identify useful bacteria and metabolites that help prevent or improve pathologic conditions. Moreover, to explore the biological processes of gut bacteria, we conduct animal model experiments and test the hypotheses made using the MANTA platform.

＊Discovery of useful gut bacteria that may alleviate obesity and diabetes, and elucidation of their mechanism of action

Through verification of prediction proposed by MANTA platform, we discovered *Blautia wexlerae*, a useful gut bacterium with the potential to prevent or improve obesity and diabetes. *Blautia wexlerae* produce L-ornithine, acetylcholine, and S-adenosylmethionine, which act to inhibit fat accumulation and inflammation. In addition, by producing short-chain fatty acids (i.e., acetic acid), and amylopectin, which is an indigestible starch, they work with other gut bacteria to improve the intestinal environment to prevent or improve obesity and diabetes. Based on this finding, drug discovery involving *Blautia wexlerae* and their use in healthy foods could help lead to a healthy society.

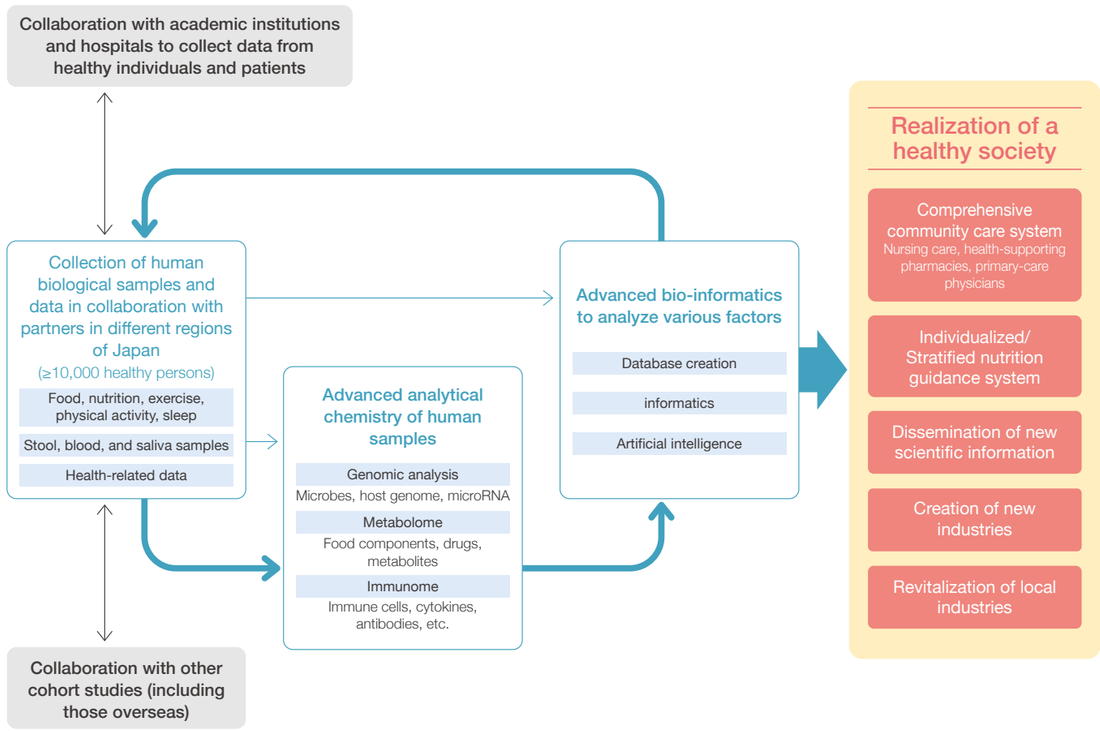
＊Relationship between cooking oil consumption and allergy or inflammation

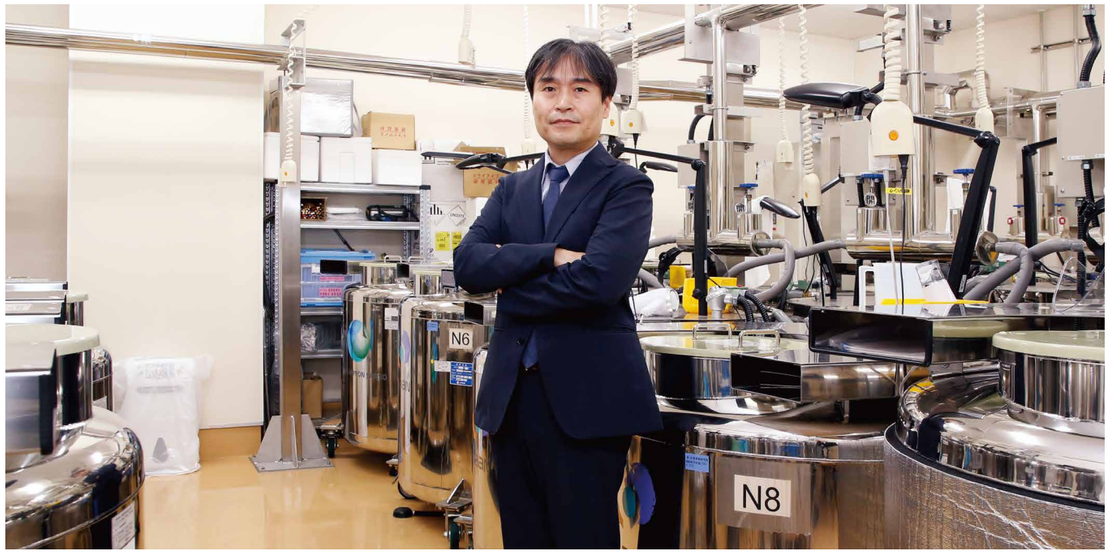
Based on our research focusing on the dietary oils, we are searching for substances that may inhibit allergies and inflammation. Our research using animal models have indicated that 17,18-epoxyeicosatetraenoic acid (EpETE), 12-hydroxyeicosapentaenoic acid (HEPE), 15-HEPE, and 14-hydroxydocosapentaenoic acid (HDPA) are produced by the action of specific enzymes in various tissues after the ingestion of flaxseed oil, which potentially suppress allergies and inflammation in the intestines, respiratory organs, and skin via their own specific mechanisms.



We have also discovered that gut bacteria and microorganisms in fermented foods use oil to produce metabolites that suppress allergies and inflammation. One of them is called "*α*KetoA." It is a metabolite that only microorganisms can produce and humans cannot. In collaboration with Kyoto University and companies, we found in animal models that *α* KetoA suppresses allergic dermatitis and diabetes by preventing macrophage-mediated inflammatory response. Based on these findings, new drugs and functional foods could be developed in the future.

Figure. An Overall Framework of Intestinal Environment Research and Practical Application of Results





Center for Drug Discovery Resources Research
Center Director, Arihiro Kohara

Why did I focus on cell biology?

While synthesizing compounds on my own under the Faculty of Pharmacy at university and analyzing the effects they have on cells and animals from a chemical perspective, I became fascinated by the mystery of cells as a research tool.

Supporting drug discovery research by providing high-quality bioresources.

Development and distribution of drug discovery resources that lead to an immediate response to emergencies

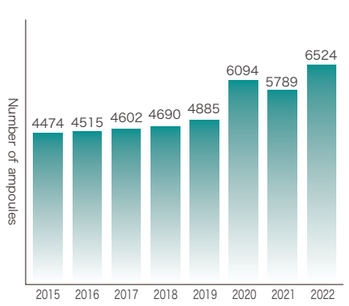
In 1985, the Center began providing various types of biological resources, including cultured cell lines, to researchers. Since then, it has collected and catalogued a number of biological resources to support basic research, and especially drug discovery research, in Japan. The Center has created a system to distribute more than 1,900 types of cell lines, and is also adding more than 40 new types of biological resources every year in an effort to meet the needs of researchers. Researchers who wish to use our biological resources can easily request them through the JCRB Cell Bank website. We have built a system in which the biological resources ordered can be delivered to researchers within the next week so that research can begin quickly. This system that helps to rapidly facilitate various types of research has grown into an operation that now distributes as many as 6,000 samples annually.

The response to the COVID-19 pandemic stands an example of how we were able to respond immediately to an emergency with our steadily maintained system of distributing biological resources. In collaboration with the National Institute of Infectious Diseases, we led the world in providing a cell line (JCRB1819: VeroE6/TMPRSS2) for use in isolating and growing SARS-CoV-2 starting in February 2020, right after the pandemic started. This enabled us to contribute to the development of a number of vaccines, therapeutics, and other products.

Changes in the number of newly catalogued cultured cell resources

FY	Number of cell lines collected	Number of cell lines catalogued
2015	79	70
2016	43	93
2017	73	56
2018	106	40
2019	47	42
2020	88	40
2021	66	44
2022	65	46
Total	**567**	**431**

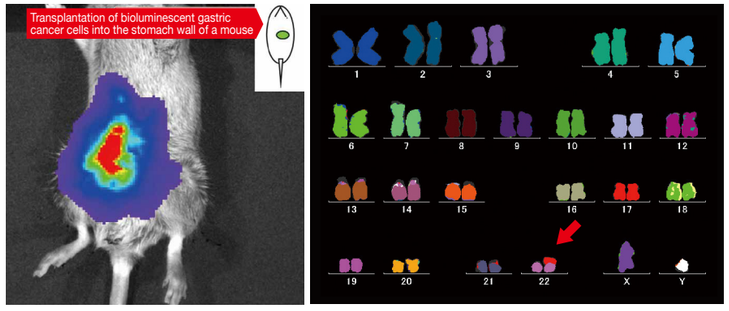
The number of distributions to researchers.



Commitment to high quality resources to maintain reliability

Compared to when the Center started providing biological resources, science and technology have advanced dramatically today, and technologies for testing cell characteristics and quality that were not available at the time are being updated and developed on a daily basis. Currently, "no infection with microorganisms such as mycoplasmas" and "no misidentification of cells in cells of human origin" are practiced by cell banks around the world to provide a minimum level of quality. However, the Center is also characterizing biological resources and conducting quality control inspections to meet the needs of the times in order to provide researchers with reliable and safe resources. Amid this, we have recently been focusing our efforts on virus screening tests in particular. We have independently developed a technology that can easily screen cells for 20 types of viruses, including DNA and RNA viruses, which were of little concern to researchers in the past, and we are implementing measures to provide cells while ensuring the safety of researchers using them.

Two of the Center's unique resources are a cell collection of bioluminescent cancer cells and a collection of cells from patients with cancer-prone genetic diseases (e.g., xeroderma pigmentosum and Fanconi's anemia). The bioluminescent cancer cells incorporate a firefly gene (luciferase) to signal the presence of cancer when the cells have been transplanted into mice. We are endeavoring to improve cells information by analyzing the characteristics of these cells and by informing users of those results so that they feel comfortable using these cells.



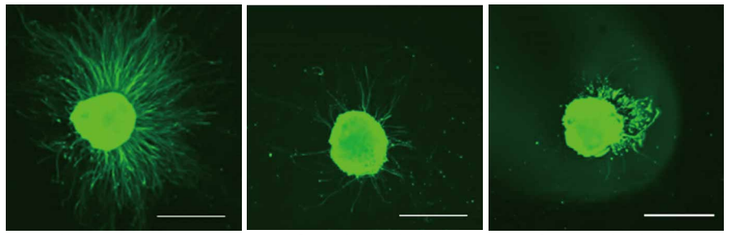
Developing novel resources for drug discovery with new technologies

The needs of users of biological resources for drug discovery have changed over time. When the cell bank was first established, users could request human cancer cell lines by specifying the type of organ from which the cancer cells were derived, i.e., "I would like cancer cells from X organ." When bioresources are obtained today, the needs have become much more sophisticated, such as the need for a profile on cancer gene mutations or for verification that target molecules are expressed and their levels of expression levels. The Center is also working to develop new bioresources in response to the needs of the times.

Catalogued cell bank resources, which mainly consist of cancer cell lines cultured two-dimentionaly in containers, cannot accurately mimic three-dimensional "cancers" in the human body. This is mainly due to the fact that the cell lines have been developed based on the "ease with which the cells are handled" since only cancer cells with the proliferative potential suitable for cell culturing conditions are passaged and grown. Such easy-to-handle cell lines are cryopreserved and used by many researchers as a research tool because they can be used repeatedly and reproducibly. However, the limitations on developing drugs using only cells that are easy to handle has become evident in drug discovery research today, and there is a growing need for research tools that are more like living organisms and pathologies. When cancer patients previously underwent surgery, the tissue was removed and then discarded. However, the Center is creating a Human Tissue Bank so that consenting surgical patients can provide researchers with cancer tissue and tissue around the cancer. We are also developing technologies to prepare cells from removed tissue and to fabricate and culture organoids three-dimensionally in vitro. This will allow some drug discovery research to be conducted under conditions more like those in living organisms and more like actual pathologies. So far, we have used these technologies to develop models needed for drug discovery research, such as an experimental system to model drug absorption in the intestinal tract and an experimental system to model drug metabolism in the liver. We are also developing more advanced models for drug discovery research that combine methods of efficiently inducing the differentiation of stem cells (such as human iPS cells) into target cells and technologies such as genetic modification. This approach has been used to prepare vascular endothelial cells to model the blood-brain barrier. Such functional cells should be able to serve as useful models of the central nervous system for drug development.

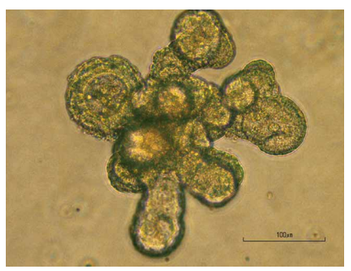
In order to more efficiently utilize various organoids and modeling systems, including those newly under development, for drug discovery, we must prepare the right amount when needed while maintaining each function. Utilizing our experience in operating the cell bank and the knowledge gained from this experience, the Center is conducting research and development of cryopreservation technologies that can store and use these cell masses in a state that retains their original functions. This will be achieved through the development of cell cryoprotectants and freezing device. In order to accelerate this research, we are actively collaborating with universities and companies to promote multiple joint research projects.

Neurite outgrowth of iPS cell differentiation-induced neurons after thawing



New freezing method | Conventional method 1 | Conventional method 2

Organoids prepared from the intestinal tract



Facilities for preparation/storage of biological resources

Safety cabinet | CO2 incubator | Ampoule sealing machine | Resource storage ampoules | Liquid nitrogen cryo sample storage | External liquid nitrogen tank

Research Center for Medicinal Plant Resources
Center Director, Kayo Yoshimatsu

Prior to starting research on plants

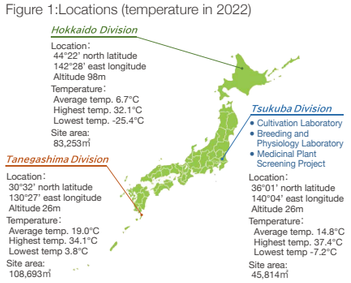
After passing the national civil service examination, I was hired as a researcher in the Breeding and Physiology Laboratory of the Center, which was a national research institute at the time, and started biotechnology research on medicinal plants. I was and still am fascinated by the mysterious power of plants.

Maximizing the potential of medicinal plants to benefit people's health in the future

Enabling the broad use of medicinal plants in Japan

Medicinal plants have been used in pharmaceuticals since ancient times. They are also indispensable for the research and development of pharmaceuticals, including Western medicines. Japan, however, must rely on imports of these medicinal plants from China and other countries, as only about 10% of the raw materials of crude drugs produced from medicinal plants are sourced from inside the country. The Center cultivates and preserves more than 4,000 strains of medicinal plants according to vegetation at three locations in Japan (subarctic, temperate, and near subtropics) (Figure.1). We regard medicinal plants as important assets and believe that it is our responsibility to make them available when needed and to pass them on to future generations. We are conducting various research to achieve this. In addition, we supply seeds and seedlings to research institutes in Japan and provide instructions on their cultivation techniques.

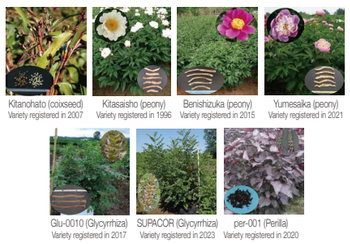
Figure 1:Locations (temperature in 2022)



Preserving northern plants and breeding of superior medicinal plant varieties using an expansive field (Hokkaido Division)

The Hokkaido Division has planted more than 1,000 strains of medicinal plants, mainly those that grow in cold regions, in herbarium garden, arboretum, useful plant garden for the Ainu people, and research field. These plants are used for research on the cultivation of medicinal plants and research and development of pharmaceuticals, functional foods, and others. We have also been working on breeding medicinal plant varieties suitable for the production of pharmaceuticals. So far, we have bred and registered a total of seven medicinal plant varieties such as coixseed, peony, glycyrrhiza, and perilla (Figure.2). A medicinal variety of coixseed known as 'Kitanohato', which can be cultivated even in cold regions, has been successfully produced in Hokkaido. It is widely used not only for pharmaceuticals, but also for quasi-drug lotions and edibles. A medicinal variety of peony called 'Benishizuka' is actually produced in Okayama Prefecture, and 'Yumesaika' in Akita Prefecture. We are developing cultivation techniques, such as optimization of fertilization and planting conditions, mechanization of weeding and harvesting work, and testing expanded applications of registered pesticides. We are also attempting to create cultivation manuals and disseminate them to production sites.

Figure 2:Medicinal plants bred and registered as medicinal varieties at our Center



Research on germination conditions of medicinal plants (Cultivation Laboratory, Tsukuba Division)

Recently, there has been a rapid decline in wild plant genetic resources. The Cultivation Laboratory of the Tsukuba Division stores seeds at low temperatures in order to preserve valuable plant resources. Seeds will not germinate if the storage conditions are not suitable, and the optimal storage conditions vary according to the plant species and varieties. Seeds of wild and cultivated species are sealed in cans or polystyrene jars and stored for long term at 10°C, -1°C and -20°C. This allows us to examine the optimal storage conditions for different plant species and varieties. To confirm the survival of seeds, we regularly conduct germination tests of preserved seeds. For those whose germination rate has decreased, we continuously conserve genetic resources by reproduction of seeds. As part of international academic cooperation, we have been engaged in seed exchanges with overseas botanical gardens for more than 70 years (Figure.3).

Figure 3:Seed storage (top left, bottom left), germination test (top right), Index Seminum (seed list) sent to overseas botanical gardens (bottom right)

Plant biotechnology contributing to the stable supply of medicinal plant resources (Breeding and Physiology Laboratory, Tsukuba Division)

In order to realize a safe, secure, and stable supply of important medicinal plant resources, the Breeding and Physiology Laboratory of the Tsukuba Division conducts research on the maintenance, preservation, and quality improvement of medicinal plant resources using plant biotechnology, and their application in pharmaceutical production. Plant tissue culture is a core technology of plant biotechnology that utilizes the ability of plants called "totipotency" that allows plants to regenerate into a complete plant from any part. The Breeding and Physiology Laboratory uses this technology to cultivate and maintain a wide variety of plants, each with the same genetic background, as "clones" of 300 species and strains in an aseptic environment. These plants are expected to play an important role as a source of healthy and high-quality seedlings of important medicinal plants required for domestic production (Figure.4).

Figure 4:Plant tissue culture (top) (middle: *Panax ginseng*, right: *Bupleurum falcatum*) and planting work on a clean bench (bottom)

Preserving tropical, subtropical and temperate medicinal plants and Leading commercial production of those difficult to obtain (Tanegashima Division)

Tanegashima has many plant species and varieties including southern limit, northern limit and rare plants and many of those are used as medicines. The Tanegashima Division preserves and propagates these medicinal plants. Some crude drugs are difficult to obtain from overseas and should be produced domestically, such as *Rauvolfia serpentina*, which is used in the traditional Indian medicine of Ayurveda and whose roots are also used in Japan for its hypotensive effect. Currently, this species is listed in CITES Annex II due to declining stocks in India, a major production area. This makes it impossible to obtain the plant from overseas. Since 1950s, the Center has preserved and cultivated the species in the fields of the Tanegashima Division. Currently, we are trying to establish a sustainable crude drug production system for *Rauvolfia serpentina* by reducing labor and enhancing efficiency in each process, from seed to crude drug production. A stable supply of *Rauvolfia serpentina* preparations is helpful to reduce hypertension (Figure.5).

Figure 5:Examples of native medicinal plants in Tanegashima (top:*Artemisia capillaris, Citrus tachibana, Prunus persica*) and an example of difficult-to-obtain medicinal plants (bottom:*Rauvolfia serpentina)*

Artemisia capillaris
Medicinal part:capitulum
Indications:Choleretic, anti-inflammatory, diuretic

Citrus tachibana
Medicinal part: pericarp of mature fruit
Indications: aromatic stomachic, antiemetic, antitussive, expectorant

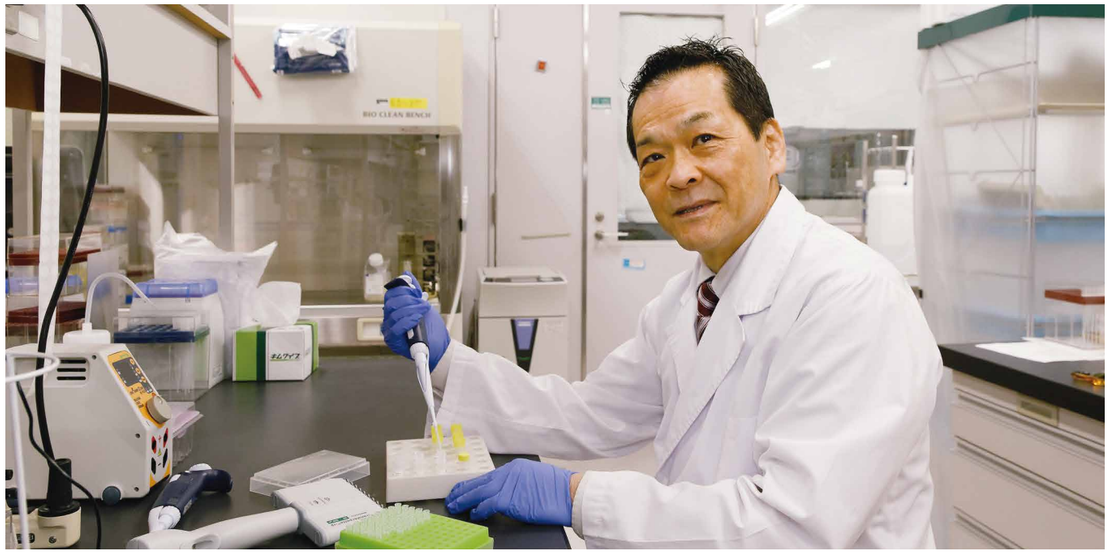
Prunus persica
Medicinal part: seeds and leaves
Indications: antibacterial, anti-inflammatory and anti-blood-stasis, drainage, emmenagogic, laxative

Rauvolfia serpentina
Medicinal part: roots
Indications: hypotensive, sedative

Medicinal plant screening project

Our planet is believed to contain some 270,000 plant species. However, the use of natural resources overseas is becoming more difficult every year due to the Convention on Biological Diversity and other factors. In this project, more than 10,000 extracts (representing more than 3,000 plant species in terms of scientific name) prepared mainly from plants growing in Japan are stored and maintained as dimethyl sulfoxide (DMSO) solutions at -20°C. They are provided to research institutions in various research and development fields such as pharmaceuticals, cosmetics, health foods, and agrochemicals, and so on. Our eventual goal is to commercialize the actual products utilizing these extracts.

Figure 6:Collection of wild plants (top) (left, middle), extraction equipment (top right), and DMSO solution of plant extracts stored at -20°C (bottom left) and biological activity evaluation using plant extract library (anti-cancer activity evaluation: bottom middle, right))



Tsukuba Primate Research Center
Center Director, Yasuhiro Yasutomi

Day-to-day research activities

Research using Nonhuman Primates (NHP) covers many areas, from basic research to practical applications in medicine, with the ultimate goal being disease control. In this way, medical science research using NHP aims to control diseases starting with basic research and shed light on the final phase of disease overcome. To reach this future goal, we are building drug discovery technology platforms, conducting research on the creation of animal models for human diseases using NHP, and furthermore, the development of vaccines with the best possible effects on global public health.

Supplying Quality Nonhuman Primates for Medical Research and Using them to Conduct Independent Medical Research

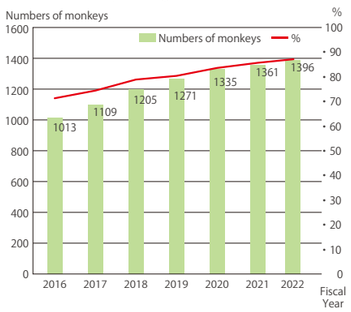
NHP for medical experiments are essential for drug discovery

A variety of evidence is needed, from drug development and research to the provision of those drugs to society. Among these, experiments for confirming efficacy in animals before clarifying it in humans are an indispensable part of that process. Testing in NHP, which are closely related to humans, is particularly crucial to drug discovery. As the export of laboratory NHP from other countries has ground to a halt since the pandemic, NHP for medical experiments are becoming increasingly important to drug discovery in Japan.

Breeding SPF monkeys with an unparalleled pedigree to secure a population of elderly monkeys

The Center is the only facility in Japan providing cynomolgus macaques for medical science. It has established a system for maintaining and supplying quality cynomolgus monkeys as a research resource, and is conducting medical research using primates from the individual to the genetic level.
After I took up my position as the center director in 2007, we started breeding specific pathogen free (SPF) monkeys that cannot compromise research integrity. We have documented the background data, including rearing history, pedigree, and laboratory test results, of all monkeys bred at our center. The breeding building holding SPF monkeys was at 14.0% capacity in 2007, reaching 88.9% by the end of 2022, a level close to the feasible upper limit (Graph 1).
Since my appointment as director, I have been stressing the importance of planning several decades ahead to ensure a stable supply of elderly monkeys. Although this is an arduous task, elderly monkeys are a valuable research asset which is absolutely necessary in the rapidly aging world. The colonies of elderly monkeys that have been reared aseptically at our center are unparalleled in terms of quality and population.

Graph1. Chronological Changes in the Numbers and Percentages of High-Quality SPF Cynomolgus Monkeys Produced



Number of Cynomolgus Monkeys Produced and Supplied Each Year

	Category	2016	2017	2018	2019	2020	2021	2022
Number of monkeys produced		210	219	214	210	222	211	189
Number of monkeys supplied	Normal monkeys	189	187	143	196	163	154	206
	Special monkeys*	8	24	15	4	10	10	2
	Total	197	211	158	200	173	164	208

*Special monkeys include: fetuses; pregnant, elderly, and newborn monkeys; and monkeys with macular degeneration, heart disease, diabetes, etc.

Providing experimental animals and technological support to help streamline drug discovery

We do more than just supply pharmaceutical companies and academic institutions with NHP. We provide contract research services and conduct outsourced experiments using monkeys at our facilities. We accept only studies deemed appropriate by our internal evaluation committee. Besides supplying primates, we can provide researchers with a wide range of resources and services, such as computed tomography scans, anatomy, experimental skills, and expertise. Through these services, we support drug manufacturers to accelerate and reduce the cost of drug discovery.

Combating intractable diseases, rare diseases and infectious diseases with no established therapy

Our research targets diseases for which no standard therapies have been established and that should be addressed by public research initiatives. Our monkeys have well-documented pedigree records. Therefore, when monkeys spontaneously develop a certain incurable disease, we can investigate the genetic likelihood of the disease appearing in the offspring born to specific parents. For example, we have naturally developed experimental NHP models of retinal macular degeneration, dilated cardiomyopathy, and other rare diseases. These models enable us to track the disease course from their presymptomatic stages and to analyze pathological changes over time. We are also developing animal models of experimentally induced disease, focused mainly on infectious diseases.
Our recent achievements involving monkeys include the establishment of an in vivo COVID-19 evaluation system. This simian model can be used for the pharmacological evaluation of candidate COVID-19 therapies. Based on these foundations, in 2023, we reported that the coronavirus is also effective in monkeys using the ACE2 protein, which is also an infection target, as a treatment that is effective against the mutant virus (Omicron strain) for which antibodies have become ineffective.
We are also investigating a cynomolgus monkey model of vertically transmitted human T-cell leukemia virus type 1(HTLV-1) infection because this represents a disease that Japan must address. Japanese individuals account for 10% of patients infected with HTLV-1 worldwide. Japan is the only developed country with a high prevalence of this disease. The disease is vertically transmitted to infants through breast milk, and virus carriers have a 5% lifetime risk of leukemia. No cure is available, and no useful animal models of disease have existed. We succeeded in establishing the world's first primate model of HTLV-1 infection by artificially inseminating female cynomolgus monkey infected with HTLV-1. When the offspring of the infected monkeys were being weaned, we replaced them

with newborns born to monkeys that were not infected with HTLV-1. We examined whether an infection was acquired via breast milk lacking maternal antibodies. Our study using this model is in its early stages. It will play a crucial role in developing new vaccines and other drugs for HTLV-1 infection.
In addition, we have created an attenuated AIDS virus incorporating an adjuvant molecule, and we are developing and researching a vaccine technology that could lead to a cure for HIV. We are also conducting research to evaluate this technology using primates. We plan to embark on a human clinical trial after the simian study is successfully completed. While patients with AIDS currently need to take drugs for the rest of their lives, a vaccine that could cure HIV is highly anticipated by researchers and patients around the world.

Infectious Disease Experimental Facility to Support Advanced Basic Research: Animal Biosafety Level (ABSL)-3


Biosafety level (BSL)-3 laboratory


BSL-3 animal housing room


Cynomolgus monkey housing cages


Shower room

An autoclave


Biosafety suits


Wastewater processing equipment

National Institutes of Biomedical Innovation, Health and Nutrition Executive Director,
National Institute of Health and Nutrition Director,
Department of Nutritional Epidemiology and Shokuiku Chief, Hidemi Takimoto

Why I started this research

I was previously an obstetrician and gynecologist. A pregnant woman who I saw for a routine health checkup asked me, “What should I eat during pregnancy for my baby?” I was shocked because I couldn't answer. This is what led me to research nutritional science.

Promoting Lifelong Health Through Healthy Eating: Investigation and Analysis of Food and Nutrition Intake Among Japanese People

Exploring the scientific basis of nutrition for a healthier future

To clarify the health effects of diet and nutrition, our department conducts epidemiological studies on nutrition. There are several foundations for our research, including the National Health and Nutrition Survey (Photo 1) conducted annually by the Ministry of Health, Labour and Welfare. Initiated in 1945, this national survey, which has amassed more than seven decades of findings, now covers not only dietary intakes, but also daily physical activity, height, weight, blood parameters, and lifestyle factors such as smoking and alcohol consumption of the people of Japan. These results provide important scientific evidence that informs national guidelines, as well as recommendations regarding the types and amounts of nutrients that should be taken daily for healthy living. These results are also used to monitor achievement of the goals proposed in the national health promotion plan, Health Japan 21 (the 2nd term).

The Laboratory of Nutritional Epidemiology aims to establish scientific evidence to help extend the healthy life expectancy of the population, and it conducts research to ascertain the relationship between diet and non-communicable diseases and health problems using various large-scale datasets in collaboration with universities and research institutes here in Japan and overseas. We are focusing on research on the relationship between protein intake and frailty in the elderly (in collaboration with entities such as the National Center for Geriatrics and Gerontology) and on the relationship between polyphenol levels in the blood and colorectal tumors (in collaboration with entities such as the National Cancer Center Japan and Kyoto University). In the future, we will also propose a diet that takes both the environment and health into account in order to achieve the Sustainable Development Goals (SDGs).

Furthermore, our data on nutrition intake were used to develop dietary guidelines presented in the *Dietary Reference Intakes for Japanese* (Photo 2). We aim to improve those guidelines by compiling research on the people of Japan with regard to creating the scientific basis for nutritional intake, so as to prevent healthy people from suffering from diseases caused by nutritional deficiencies or lifestyle-related diseases, and also help people to prevent their current condition from deteriorating. Where evidence is lacking, we will conduct further research. The *Dietary Reference Intakes for Japanese* are used as standards in various settings, such as meals in facilities, cafeterias, and hospitals. Improving the guidelines will lead to better meals being served in schools and other settings.

Related Publications

Photo 1. *National Health and Nutrition Survey*

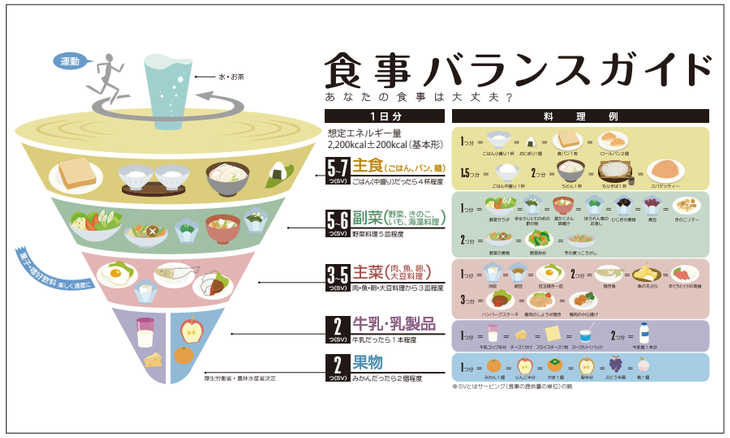
Photo 2. *Dietary Reference Intakes for Japanese*

A life-course based approach for the 100-year-life era

As described above, we are engaged in various research activities from the viewpoint of nutritional epidemiology. We are also conducting research to help people live long and healthy lives in the coming 100-year-life era, where health-related quality of life will be more valuable than mere gains in longevity. Nutritional requirements differ by different life stages and conditions. They differ between newborns and elderly people, between ill and healthy persons, and between pregnant and nonpregnant women. Children require nutrients that help them grow. Many adults need to control the risks of lifestyle diseases. Elderly people may need nutritional support to maintain and improve their physical performance and cognitive functions. This life-course based approach to physical wellbeing, involving life stage-specific nutritional interventions, is becoming more important.

In human lives, conditions in a given life stage affect the conditions in the next generation. As current children will eventually become parents, and they may face greater challenges in raising a healthy next generation if they are not healthy enough. Similarly, the health conditions in middle age will significantly determine those in older age. Focusing on the dietary patterns of pregnant and nursing women, we worked with the Ministry of Health, Labour, and Welfare to develop the *Dietary Guidelines for Prepregnant, Pregnant, and Nursing Women*, this work was done as part of the Investigation for Supporting Child Development and Rearing Program and is publicly available from NIBIOHN's website (Photo 3). We are also involved in an MHLW Scientific Research Project to examine the plans for the National Nutrition Survey on preschool children, which is conducted every 10 years to monitor the nutritional status of infants and toddlers.

Nutrition Intake Recommendations Presented in the Dietary Balance Guide



Guidelines on desirable eating habits for expectant mothers: A practical application of research findings

The purpose of this publication was to address a particular challenge identified by the National Health and Nutrition Survey. This survey reported a high prevalence of underweight (body mass index <18.5) among women in their 20s and 30s, who are in their reproductive age. There have been little improvements in this prevalence since the previous edition of the dietary guidelines was published 15 years ago. Pre-pregnancy underweight can have negative effects on pregnancy, postpartum recovery, and fetal and infant development. From the perspective of life-course management, underweight in younger ages may cause women to be susceptible to physical frailty as they grow older.

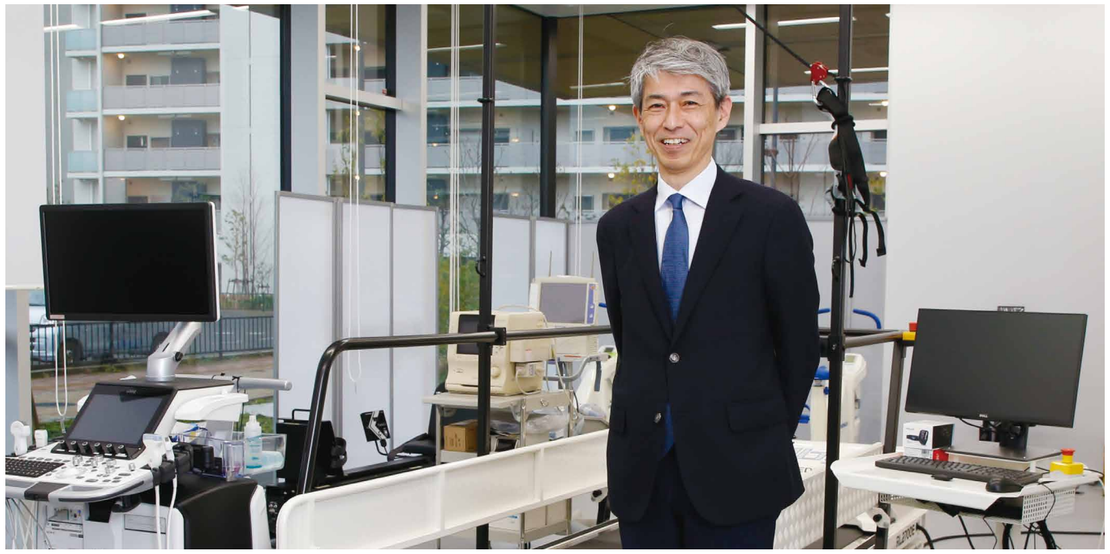
A major difference between the first and second editions is that whereas the first edition addressed pregnant and postpartum women only, the second edition also includes women expecting pregnancy, and encourages them to develop and maintain physical wellness in preparation for pregnancy. Specifically, the current guidelines have 10 key recommendations, including a well-balanced diet, sufficient energy intake from staple foods, side dishes to supplement the most commonly deficient vitamins and minerals, tips for calcium intake, and appropriate weight gain during pregnancy.

Our guidelines and recommendations are a practical help in community settings. For example, they are used by public health nurses and dieticians who support expecting mothers and babies during pregnancy and by parenting classes hosted by local health centers. They are also included in the *Maternal and Child Health Handbook* and education brochures provided by local municipalities. In these ways, the results of our research are being shared through various means and media.

Photo 3. “Dietary Guidelines for Prepregnant, Pregnant, and Nursing Women” (https://www.nibiohn.go.jp/eiken/ninsanpu/)

Academic Collaboration:
A Joint Study with Tokyo Medical and Dental University

Partly because I started my career as an obstetrician and gynecologist, my research interests include dietary intakes and placental development in pregnant women. With the assistance of the Tokyo Medical and Dental University Hospital, I conducted a cohort study in which approximately 200 pregnant women were registered and then interviewed by nutritionists to record their daily meals. Other members of the research team include dietitians, obstetricians, gynecologists, and pediatricians. Researchers at the University's Medical Research Institute conduct genetic analysis. Although clinicians understand the important role of nutrition and diet in health, they face challenges in making dietary advice in clinical practice. We hope that the findings of this study will be used in clinical practice to improve women’s health conditions.



Department of Physical Activity Research
Chief, Rei Ono

Why I decided to begin my research at NIBIOHN

Through working at the hospital, I realized the importance of physical activity for patients returning home and improving their prognosis, and I became interested in research on physical activity (exercise). NIBIOHN is the only institution in Japan that can conduct research on physical activity and reflect it in policies through guidelines, and I started working there because I thought it could greatly contribute to improving the physical activity of the people.

Improving the public's physical activity and exercise habits through guidelines on exercise and accurate assessment of physical activity

To improve people's physical activity and exercise habits through exercise guidelines

In Japan, the National Health and Nutrition Survey (known as the National Nutrition Survey until 2002) has been conducted since 1989 to assess the level of physical activity among the people of Japan. The survey uses pedometers to measure the number of steps taken by people in a day. The survey has been conducted continuously and on a large scale, and it provides important data on trends in physical activity for reference around the world. The Department of Physical Activity Research has been engaged in two major efforts to help increase the number of steps measured in the National Health and Nutrition Survey.

The first is to disseminate information to improve the public's physical activity and exercise habits. In order to share evidence-based information, academic papers on physical activity, exercise, physical fitness, and health from around the world have to be collected and analyzed (literature reviews and meta-analyses). We are researching the relationship between physical activity; exercise, and physical fitness and health outcomes. Based on the evidence obtained, we have drafted exercise guidelines such as Exercise and Physical Activity Reference for Health Promotion (EPAR) and the Active Guide (physical activity guidelines) to provide information to the public to improve their physical activity and exercise habits.

The second effort is to develop and validate methods of assessing the level of physical activity. Over the last few years, assessment of the level of physical activity, as typified by the number of steps taken, has been based on values obtained by processing signals from an accelerometer built into each pedometer. However, a pedometer can be located in various places on or near the body, such as one worn on the waist, on the arm, or built into a smartphone. In other words, even if the number of steps taken is the same, one can never know whether or not it accurately reflects the actual number of steps taken depending on the method of measurement. The Department of Physical Activity Research is verifying the validity and accuracy of the values from each model of pedometer in order to allow continuous assessment of trends in the number of steps taken according to the National Health and Nutrition Survey and to facilitate physical activity research in other fields.

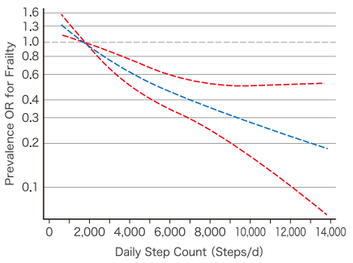
Following the spread of COVID-19 beginning in 2020, lockdowns and other restrictions on activities were imposed around the world. A survey we conducted found that the objectively observed level of physical activity was significantly lower in the Tokyo metropolitan area than in rural areas due to the declaration of a state of emergency in April and May 2020 in Japan. As evidence-based policymaking is increasingly being emphasized, we hope that monitoring changes in the physical activity of the public in this manner will continue to play an important role in policymaking at the national and local levels.

Identification of modifiable factors to prevent frailty, from research to implementation in society at large

Japan has the world's highest rate of aging, and the world is looking to see how Japan will cope with a super-aged society. As people age, their physical and mental vitality (e.g., motor and cognitive functions) declines, and their vitality can be affected by the presence of multiple chronic diseases. This can lead to impaired daily functions and greater susceptibility to mental and physical frailty. This condition is known as frailty. Frailty is a decline in daily functions common to old age, but daily functions might be maintained and improved through early detection of frailty and appropriate interventions and support. The Department of Physical Activity Research is working with local governments to ascertain the relationship between physical activity and exercise against frailty and to implement the results not only in research but also in society at large.

＊A study on healthy longevity in Kameoka City, Kyoto Prefecture

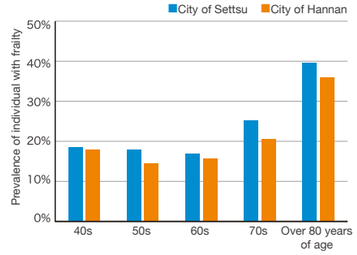
Kameoka City has developed a program to prevent the need for nursing care in the community and is testing its effectiveness. The method of the program's implementation has been verified in the short term. Elderly participants who attended a weekly exercise class were compared to a group who exercised at home to determine if either had an increase in motor function or muscle mass. The results indicated that both groups saw an increase in motor function or muscle mass. In addition, a public course was conducted to train assistants to prevent the need for nursing care in conjunction with public education about the program. Some of those assistants later established an NPO, and they have continued to provide support to the class participants even after the study concluded. In addition, research results in this field recently revealed that elderly people who walk more, who consume more protein, and who eat a higher quality diet are less likely to be frail and that elderly people with a higher or lower BMI (an indicator of one's physique) than normal are more likely to be frail. Moreover, the results also showed that people with a larger sphere of activity in daily life had a lower risk of mortality and that leaving the house to run errands in the city at least one to three times per week did not see any change in their risk of mortality. The evidence generated by the local community is helping to extend healthy life expectancy not just in Kameoka City but in the rest of Japan.



＊A study on preventing frailty among the working-age population in Osaka Prefecture

The Department of Physical Activity Research, together with the Osaka Prefectural Government, is developing a lifestyle modification program to prevent frailty. As part of the program, a survey on frailty featuring a basic checklist was conducted. Results revealed a certain percentage of both the elderly as well as working-age people in their 40s and 50s were frail and that respondents who were familiar with the term "frailty" were less likely to be frail than those who were unfamiliar with the term. In 2022, the program conducted frailty checks at companies during specified health exams. These checks revealed that a certain percentage of workers were frail. We aim to prevent frailty in the long term by increasing the awareness of frailty among the working-age population.

Assessment by the basic checklist

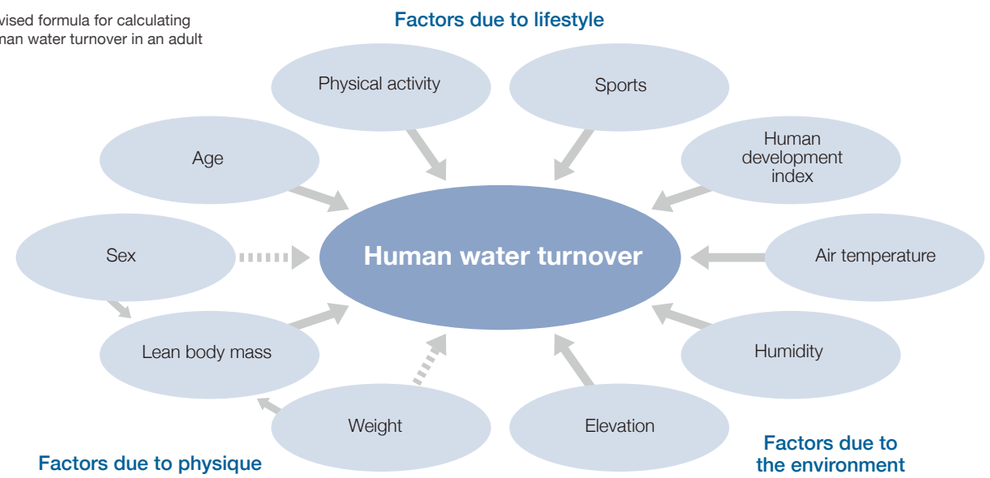


A new approach: The human water turnover

Water is constantly needed to sustain human life and to facilitate blood circulation and physical activity. Thanks to previous studies, the stock of water in the human body can be determined. Perhaps surprisingly, determining the flow of water in and out of the human body has been difficult. The Department of Physical Activity Research has integrated data measured in Japan and in various countries and it has used a technique known as the "doubly-labeled water method" to devise the world's first formula for predicting water turnover in adults. The resulting approach can be used to formulate guidelines for water intake to prevent dehydration during physical activity. This research has been published in an international journal and it has attracted worldwide attention. The United Nations estimates that about one-third of the world's population lacks safe drinking water at home and water shortages are becoming a more pronounced problem, especially in developing countries. Thus, this predictive formula could be used to formulate strategies to allocate drinking water and food in the event of a disaster or emergency in different countries and it could be used to create models to predict water shortages due to population growth and climate change around the world.

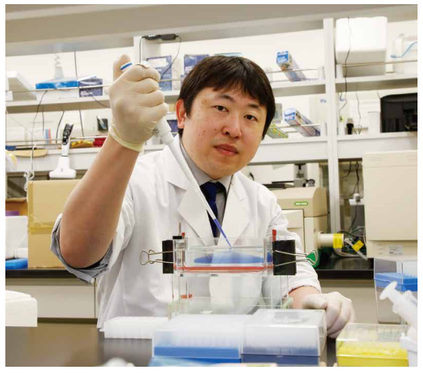
In addition, this research will open up new avenues in this field, such as examining the relationship between dementia and frailty and the metabolic turnover of water

The devised formula for calculating the human water turnover in an adult

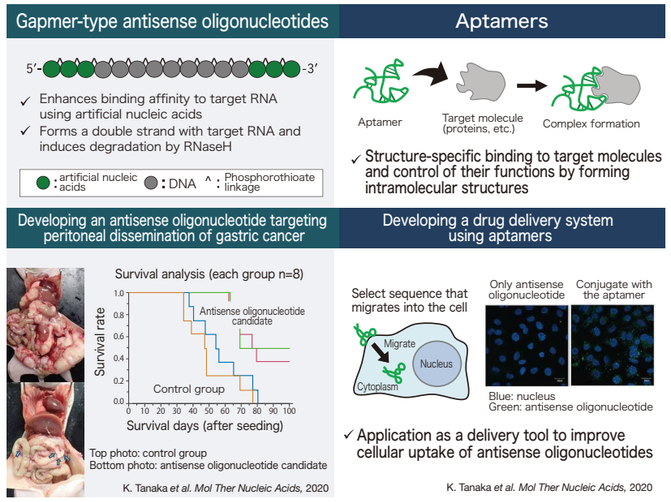


Capitalizing on an engineering perspective to develop nucleic acid drugs with limitless potential!

I started my research activities at NIBIOHN soon after obtaining my degree from the Graduate School of Engineering. I have been developing nucleic acid drugs with the hope of making a difference in the lives of patients suffering from incurable diseases without any known effective treatment option.
There are two types of nucleic acid drugs: antisense oligonucleotides and siRNAs that act on nucleic acid molecules, and aptamers and decoy nucleic acids that act on proteins. By taking advantage of the characteristics of each, all molecules in the body can be targeted for drug discovery. Therefore, in theory, there are no restrictions on the target disease. This is the greatest appeal of nucleic acid drugs.
So far, we have succeeded in improving the functionality of aptamers by introducing artificial nucleic acids (xeno nucleic acids; XNAs) and developing new methods to create them. We have also designed and developed highly active and low-toxicity antisense oligonucleotides from an engineering perspective, and created therapeutic drug candidates for intractable diseases. Antisense oligonucleotides for peritoneal dissemination of gastric cancer are in the final stage of pre-clinical testing. We are conducting research so that they can be delivered to patients as soon as possible.

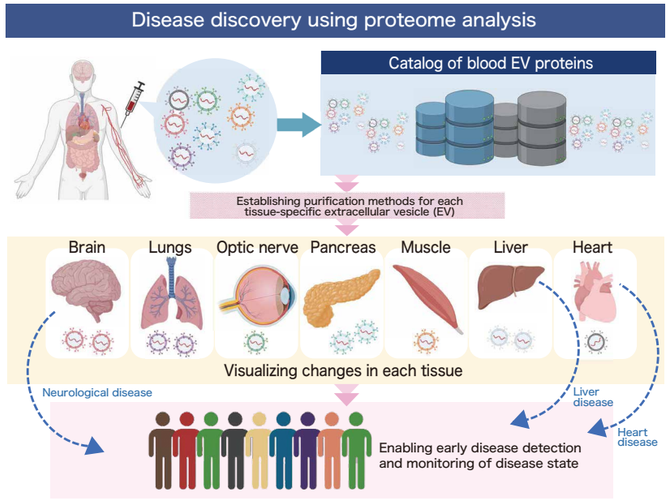


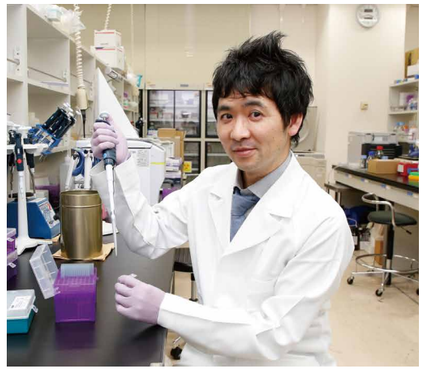
Laboratory of XNA Screening and Design
Center for Drug Design Research
Project Leader **Yuuya Kasahara**



Focusing on exosomes in the blood, we are developing technologies for less-invasive approaches to diagnosis and pathology monitoring

When I was studying abroad, I came across neurological disease research, and I was intrigued by the difficulty and interesting nature of the field. Neurodegenerative diseases are important diseases in Japan, where the population is aging. Many therapeutic drugs are expected to be developed in the future, but the key is being able to stratify patients who respond to treatment.
In recent years, exosomes circulating in the blood stream have been in the spotlight in the development of biomarkers. Diagnosis by blood is minimally invasive, and there is a strong likelihood that changes in the pathology can be detected instantaneously.
Through proteomic analysis of blood exosomes, we identified candidate tissue-specific exosome markers. We believe that the establishment of brain-derived exosome purification technology will lead to the diagnosis and suppression of the onset of neurodegenerative diseases. Although challenges are emerging one after another, I am conducting research with the excitement of discovering unknown phenomena with the priority of rolling out my findings for patients as soon as possible.



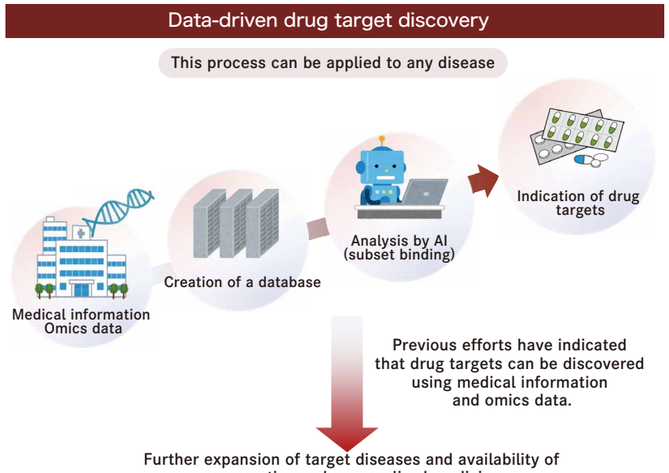


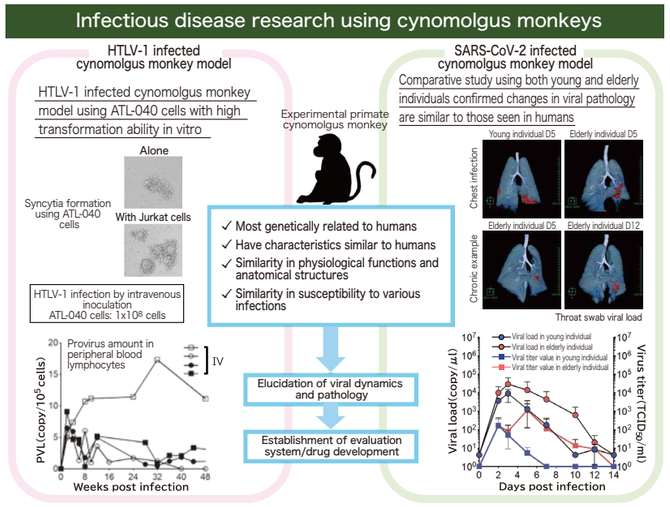
Laboratory of Proteomics for Drug Discovery
Center for Drug Design Research
Senior Researcher **Satoshi Muraoka**

Utilizing differing macro- and micro-level information to conduct data-driven drug target discovery

The inability to confirm the efficacy of drugs in human is the culprit behind the high rate of failure in many clinical trials. In response, we have started the development of technologies and data analysis methods for drug discovery targeted searches utilizing human derived medical information and omics data.
While the acquisition of medical information (macro-level information at the individual level) and omics data (micro-level information at the molecular level) is significant, the content and format of the two are different, and it is difficult to determine a connection between them through analysis. Therefore, we developed an analysis technology with RIKEN that can find related item groups. In joint research with Osaka University, we succeeded in finding drug discovery target candidates and their inhibitors for idiopathic pulmonary fibrosis.
We believe that this approach can be applied to all diseases. Especially in the case of intractable diseases, we can search for important factors without relying on previous knowledge. This is why I feel a deep sense of calling in fulfilling the hopes of patients who are suffering.

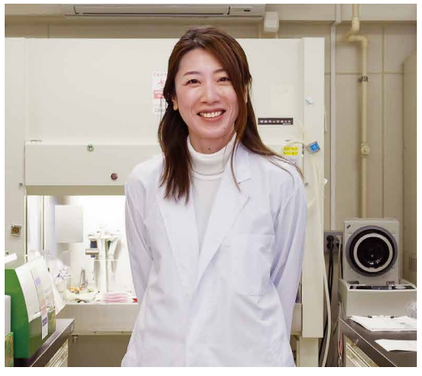
Laboratory of Bioinformatcs
Artificial Intelligence Center for Health and Biomedical Research
Project Leader **Yayoi Natsume**





Working on unique and important research using primates only possible at NIBIOHN

When I arrived in 2016, I became involved in primate research. I was fascinated by the clever survival strategies of viruses, and although I have been mainly researching HIV since my university days, I had no experience in conducting experiments with animals, so I started off somewhat perplexed.
I was first involved in a study to establish a primate model for HTLV-1. HTLV-1 is a retrovirus, as is HIV, but because of its distinctive characteristics, we set up an analysis method and launched primate experiments in parallel. As a result, we established the world's first HTLV-1-infected nonhuman primate model.
As for COVID-19, an elevated risk of severe illness has been reported in the elderly. By adding elderly primates, which are a valuable research resource worldwide, we have shown that the cynomolgus monkey model reflects the human COVID-19 pathology well.
Both models are also useful as evaluation systems for drug development. We are now evaluating the efficacy of multiple vaccines and therapeutics. In the future, we will continue to pursue research responsibly that is the cornerstone of preclinical studies and can only be performed by us at NIBIOHN.



Tsukuba Primate Research Center
Senior Researcher **Emiko Urano**

Introduction of researchers playing an active role in each NIBIOHN laboratory

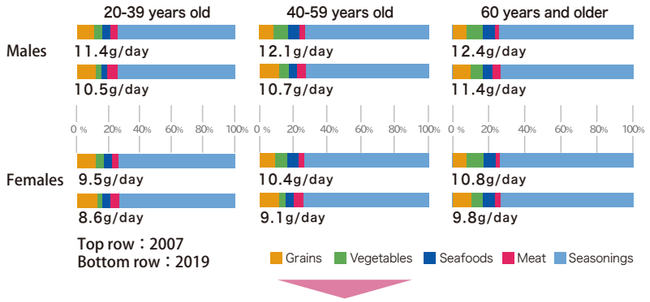
Research on Related factors influencing appropriate dietary behaviour for healthy eating habits
With the enactment of Japan's Basic Act on Shokuiku (Food and Nutrition Education), I have asked myself the question, "What is effective dietary education?" and have been examining factors related to the diets and eating behavior among Japanese. In particular, my starting point was the desire to elucidate the influence of nutrition knowledge on diet.
First, I started developing a questionnaire to evaluate the nutrition knowledge for Japanese adults . I initially struggled somewhat because I had to review materials from Japan and other countries. However, the completed questionnaire is now widely used and I am pleased that I developed it.
Currently, I have also been examining factors related to diet by life stage and course and the appropriateness of nutrient intake for the working population. In addition, I have been evaluating the appropriateness of nutrition and food information spread on social media.
Additionally, I am engaged in research to realize healthy eating habits by examining food issues through verifying the accuracy of the National Health and Nutrition Survey and supporting the formulation of health promotion plans.

Section of the National Health and Nutrition Survey
Department of Nutritional Epidemiology and Shokuiku
Head Mai Matsumoto

Examination of factors related to Japanese diet and eating behavior

Do the sources of salt intake differ among Japanese adults by age?

Participants: 95,581 Japanese adults over 20 years old who participated in the National Nutrition and Health Survey from 2007 to 2019 (43,129 males, 52,452 females)



Salt intake from seasonings accounts for 70% of salt intake for all ages

Matsumoto M, et al. Br J Nutr. 2022;129(4):1-14.

Components of human water turnover

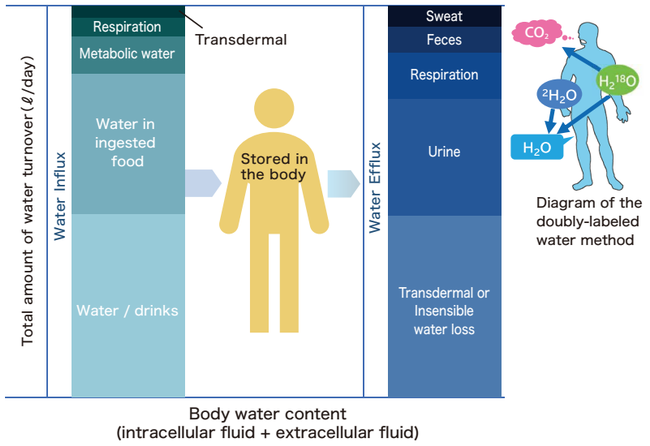


Diagram of the doubly-labeled water method

Body water content
(intracellular fluid + extracellular fluid)

Conducting the world's first research on water turnover in humans to tap into new fields of research

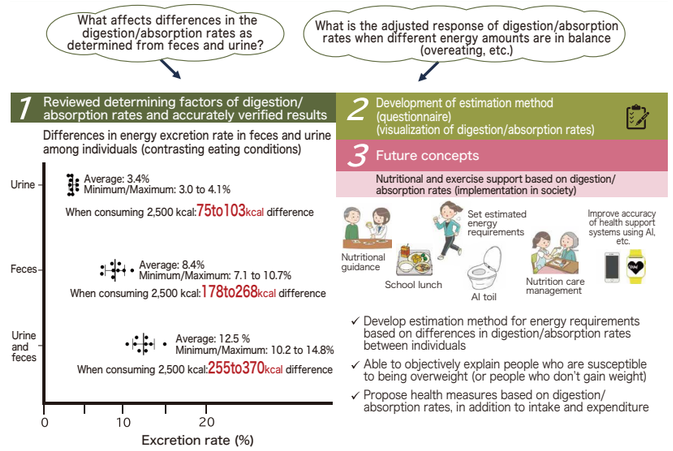
There is an especially important technology called the "doubly labeled water (DLW) method" that calculates the total daily energy expenditure, which also leads to the measurement of physical activity levels. As one of the world's leading laboratories for the DLW method, we have accumulated data from more than 10,000 people in 40 countries in collaboration with research institutes around the world with the support of the International Atomic Energy Agency (IAEA). We also published the world's first formula to predict human water metabolism.
In addition, I have been studying the relationship between skeletal muscle and water since I was a university student through my own experience in sports. Skeletal muscle is 75% water and is an important reservoir of water for humans. Previously, we have shown that intracellular fluid in skeletal muscle decreases with aging and that it is related to skeletal muscle quality, muscle and physical function. While learning more about the principles of the DLW method, we have clarified for the first time the determinants of the amount of water turnover in humans using the IAEA database. Currently, I am researching the relationship between water, health, and aging. I hope to create and pioneer a research field that is unparalleled in the world.

Section of Exercise Guideline
Department of Physical Activity Research
Head Yosuke Yamada

Conducting research focused on digestion and absorption linked to more accurate health management

The energy we see in our daily lives originates in our food, minus the energy excreted from the body. The digestion and absorption rates are set uniformly regardless of gender, physique, or other factors. Although, there are individual differences in the ability to digest and absorb. For highly accurate health management, it is necessary to precisely estimate the energy requirements by an individual based on their ability to digest and absorb.
With the motivation of wanting to know the digestive and absorption capacity of people who are skinny but big eaters, I launched my current research with the support of many people. During this research, We evaluated absorption energy and excretion energy by the method of evaluating physical energy from the changes in water temperature in an aquarium by completely combusting samples (food, feces, urine, etc.) in an oxygen-filled cylinder, we found that there were non-negligible individual differences in the latter that could not be ignored. While there are still obstacles to overcome, we continue my research with the aim of contributing to a society where it is possible to conduct highly accurate health management according to individual characteristics.

Overview of Research (Aim of Research on Digestion/Absorption Rates)



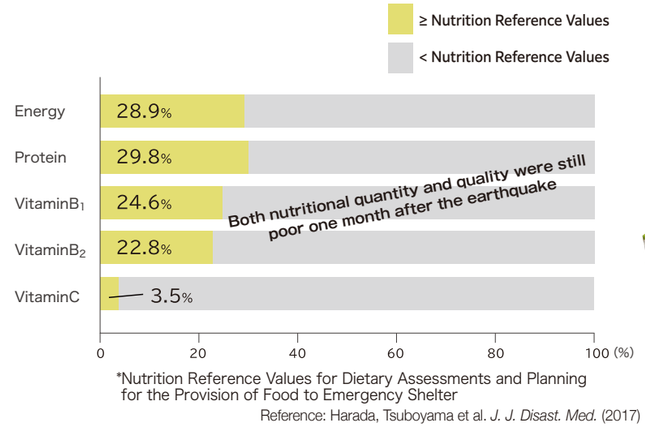
Section of Energy Metabolism
Department of Nutrition and Metabolism
Head Eiichi Yoshimura

Refining my specialization in disaster nutrition to create evidence that can be utilized in future disasters

When I was in university, I met a world-leading female researcher at NIBIOHN, who taught me that "expertise that is second to none" is important for social independence. I was also keenly aware of the need for food and nutrition research in the event of a disaster, and thought about what I could do for people living in disaster-prone countries. With disaster nutrition as my specialization, I decided to work at NIBIOHN, because I admired its high-level research.
I have shown in my previous research that the quantity and quality of meals improved after the Great East Japan Earthquake by increasing the frequency of mass feeding for evacuees and having menus prepared by registered dietitians. Currently, I am researching the relationship between malnutrition and health problems after disasters. When a disaster occurs, I immediately collect information on the affected areas and provide food and nutrition support.
I felt worthwhile when the evidence generated by my research was used in the training of dietitians for disaster support. There are some birth pangs, but I will do my best to create a future where there are no health hazards caused by food and nutrition in the event of a disaster.

Results of fact-finding survey on the Great East Japan Earthquake

Percentage of emergency shelters that met nutrition reference values* (n=114)



*Nutrition Reference Values for Dietary Assessments and Planning for the Provision of Food to Emergency Shelter

Reference: Harada, Tsuboyama et al. *J. J. Disast. Med.* (2017)

Section of Global Disaster Nutrition
International Center for Nutrition and Information
Researcher Moeka Harada

Priority Diseases

Laboratory of Therapeutics for Intractable Diseases

We operate the National Database of Designated Intractable Diseases of Japan, based on clinical research forms for about one million patients per year. By registering and providing the extensive patient clinical data, we support research and development in the area of intractable diseases.

Laboratory of Rare Disease Information and Resource Library

Seeking to promote drug discovery for rare and intractable diseases through utilization of information and resources, we are analyzing drug target genes/pathways based on clinical trial data and constructing their database, as well as operating a biobank collaborating with patient registries and analyzing the resources.

Reverse Translational Research Project

This Project is implementing a reverse translational approach in which various questions that arise in clinical practice are translated into basic research subjects and answered. Researchers are working to elucidate the pathogenesis of intractable diseases and to analyze data on intractable diseases using machine learning, and they will use the results of that research to solve clinical problems.

Laboratory of Vaccine Materials

Focusing on the immune system of mucosal tissues, the Laboratory is conducting research to develop vaccines, immunotherapies, and healthcare products to prevent and alleviate infectious diseases, allergies, inflammatory diseases, and lifestyle-related diseases. As examples, researchers are developing vaccines and diagnostic systems to combat bacterial food poisoning and adjuvants created using components of intestinal bacteria.

Laboratory of Precision Immunology

We aim to achieve personalized and stratified medicine using immunological approaches to overcome intractable diseases, including cancers, chronic infections and neurodegenerative diseases. We will advance the understanding of accurate immune status changes for each donor through multilayered immune omics analysis, and develop disease-specific surrogate marker exploration, as well as vaccines and immunotherapies.

Laboratory of Immunogenomics

In order to provide precision medicine with the optimal treatment for individual patients, our Laboratory is identifying the pathogenesis and biomarkers of diseases based on multi-omics data, mainly using genomic and immunogenomic analyses. We also seek to develop novel immunotherapies based on patients' genomic information.

Laboratory of Cell Vaccine

Several cell vaccine therapies that use dendritic cells and chimeric antigen receptor T cells have reached clinical stages. Given that functional cell vaccines are a promising future modality, research pursues the methods for creating and using them for therapy.

Laboratory of Gut Environmental System

Focusing on the intestinal environment created by symbiotic microorganisms (such as intestinal bacteria) and food components, the Laboratory is performing human and animal studies to ascertain the relationship between the intestinal environment and health and disease. The results will be used to develop new drugs and health care products.

Laboratory of Gut Microbiome for Health

Research focuses on the role of gut microbiome in the relationship between lifestyle factors and healthy conditions including frailty, and aims to build evidence for extending healthy life expectancy, taking note of metabolic and chrono-nutritional perspectives.

Drug Discovery Platforms

Laboratory of Proteomics for Drug Discovery

We are developing state-of the-art proteomics technology for large-scale clinical proteomic analysis in order to develop new biomarkers and treatment methods. Furthermore, large-scale data sets are used to elucidate pathological mechanisms and to discover new biomarkers and therapies.

Laboratory of Antibody Design

The overall goal of the project is to create next-generation antibody therapies with maximum efficacy. We are conducting research on establishing new classification concepts and designing methods of antibody-binding site (epitopes) structures under in vivo environments that determine the function of antibodies as therapeutic agents.

Laboratory of XNA Screening and Design

The Laboratory is working to create new nucleic acid-based drugs by synthesizing artificial nucleic acids (xeno nucleic acids: XNA), designing sequences containing XNAs, isolating target-specific nucleic acid molecules via screening, evaluating their functions, and optimizing them for their intended use.

Laboratory of Drug Discovery Imaging

Focusing on the dynamic immune network, research explores the fundamental principles that regulate and maintain the functional integrity of organs and tissues. Knowledge about these principles will help create innovative drugs.

Laboratory of Biofunctional Melecular Medicine

The project is investigating the biofunction of 'cancer-related genes' identified via comprehensive omics analyses in cancer elucidating the molecular mechanisms of cancer development and resistance to treatment and developing therapeutic approaches through the biofunctional regulation.

Laboratory of Nuclear Transport Dynamics

To develop new drugs with novel mechanisms of action, researchers investigate the pathogenetic mechanisms underlying various disorders from the perspective of nucleocytoplasmic transport of macromolecules.

Laboratory of Advanced Biopharmaceuticals

Basic technologies are being developed to create novel biopharmaceutical modalities using techniques such as protein engineering, antibody engineering and synthetic organic chemistry. We are developing new technologies to create biopharmaceuticals with greater functionality than existing antibody drugs, mainly modified antibodies.

Biological Materials

Laboratory of Drug Discovery Resources Research

The Laboratory operates the JCRB cell bank, which has the largest number of cell samples in Japan, and a human tissue bank, which provides tissue leftover from surgery to researchers in Japan. The laboratory facilitates drug discovery research in Japan and abroad by providing quality biological resources. We are also working to develop tools required for drug discovery research.

Laboratory of Cell Model for Drug Discovery

Activities seek to develop efficient methods that differentiate stem cells into functional cells using the knowledges of embryology and molecular biology, and to create novel drug discovery platform technologies (e.g., screening systems) using engineered functional cells.

Laboratory of Functional Organoid for Drug Discovery

To accelerate drug discovery, new in vitro systems are developed using cells (e.g., hepatocytes and intestinal epithelial cells) that are differentiated from human induced pluripotent stem cells. These systems are used to predict drug efficacy and toxicity.

Laboratory of Drug Discovery Resources Research Collaboration Promotion Office

To accelerate drug discovery research, we are developing efficiently resources of evaluation system models by using cells with some function or with a disease phenotype through internal and external collaborations.

Laboratory Animal Resource Bank

The Laboratory develops small animal models of diseases essential for the study of diseases, including intractable diseases. We also operate an animal research resource bank for testing and the development of treatments. The laboratory facilitates disease research and drug discovery by developing and analyzing models, collecting, storing, and supplying animals with spontaneous diseases and genetic modifications, and developing related technologies.

Research Center for Medicinal Plant Resources

As the sole comprehensive research institution for medicinal plant resources in Japan, this center conducts research on cultivation techniques, new plant breeding approaches, and methods for the evaluation and application of medicinal plants. This center cultivates and maintains more than 4,000 strains of medicinal plants at three sites in Japan (Hokkaido, Tsukuba, and Tanegashima), it provides many research organizations with seeds, seedlings, and plant extracts, and it provides technical guidance.

Tsukuba Primate Research Center

We have the only facility in Japan where everything from breeding of cynomolgus monkeys to research and development can be done consistently. In addition to promoting research and development related to drug discovery and treatment using high-quality cynomolgus monkeys, we develop, manage, and supply new cynomolgus monkey research resources.

Unit for promotion of shared equipment experiments

We are promoting the operation and sharing of research equipment that supports cutting-edge research, with the aim of responding to diverse research needs both inside and outside the organization.

Management of Laboratory Animals

Proper management of the animal facility in the Osaka Saito area, support for animal experimentation, and assistance for animal experimentation committees are provided.

Interdisciplinary Collaboration

Laboratory of Bioinformatics

To promote data-driven drug target discovery, machine learning and other recent technologies are being used to develop new analysis methods and to analyze disease-related data (clinical information and omics data).

Laboratory of In Silico Design

Informatics and molecular simulation techniques are employed to elucidate molecular recognition mechanisms in biological systems. Research topics also include efficiently designing candidate drugs, screening for drug targets, and predicting drug efficacy, pharmacokinetics, and toxicity.

Laboratory of Toxicogenomics-Informatics

The Laboratory is conducting basic research on drug discovery related to the identification of pharmacological/toxicological biomarkers, the development of systems to predict toxicity, and the elucidation of the mechanisms of adverse drug reactions by using next-generation sequencing-based transcriptome analysis and AI technology.

AI Nutrition Project

In collaboration with institutions inside and outside, cohort data, measurement data, and other evidences are accumulated to develop AI/machine learning technologies and knowledge base for health, nutrition, and metabolic data.

Laboratory of Clinical and Analytical Chemistry

We are developing unique separation columns and functional probes using nano- and micro-material synthesis technologies to improve our fundamental measurement capabilities and develop new enrichment and analysis technologies for clinical application.

Food and Nutrition

Section of National Health and Nutrition Survey

The Section is working to tabulate and analyze the National Health and Nutrition Survey data conducted annually by the MHLW. In order to help promote national policies such as Health Japan 21 (the 2nd term), the Section conducts research using the data from the National Health and Nutrition Survey and it disseminates information via NIBIOHN's website.

Section of Nutritional Epidemiology

In order to establish evidence to help extend the healthy life expectancy of the population, the Section is conducting epidemiological studies on the association between diet and non-communicable diseases and other public health problems, using data from large-scale cohort studies and the National Health and Nutrition Survey. We collaborate with colleagues from other research institutions in Japan and abroad.

Section of Dietary Guidelines

The Section is conducting epidemiological studies, reviews, and other research in collaboration with domestic and international partners to establish the evidence needed to improve nutrition-related guidelines such as the Dietary Reference Intakes for Japanese, which are standards for nutrient intake necessary to maintain and improve health.

Section of Nutritional Therapy

In order to elucidate the optimal nutrition of mothers and children from pregnancy to infancy, we conduct detailed research to better understand the nutritional intake, physical condition, and health of pregnant women and babies.

Section of Food Component Analysis

This section is responsible for the food labeling regulated under the Food Labeling Act and the Health Promotion Act. It inspects food products by chemical analysis to verify whether they contain the nutrients and functional components coincident with the labeled values. In addition, this section conducts research to ensure that nutritional labeling is accurate and suitable.

Section of Food Safety and Function

The Section conducts research to assess the health effects of functional food ingredients and materials that are widely used as health foods. We also conduct research studies on people focusing on the effects of meals and health foods, in order to provide scientific evidence on safety and function of health foods.

Section of Information Network of Health Food

The Section continuously collects health information based on scientific evidence and provides information to experts and the public. The Section also conducts research to ensure effective communication of the benefits and potential risks of food products.

Physical Activity and Metabolism

Section of Exercise Guideline

The Section is conducting research to provide the scientific basis required to formulate and revise the Exercise and Physical Activity Reference for Health Promotion and the Active Guide (physical activity guidelines), which indicate the level of physical activity and amount of exercise necessary to prevent lifestyle-related diseases and cancer and to prevent the impairment of daily functions by conditions such as dementia and musculoskeletal disease.

Section of Behavioral Physiology

The Section is conducting research to verify the validity of methods to assess lifestyle (diet and physical activity) and to ascertain the relationship between lifestyle and health. Genetic, physical, psychological, and other factors determine human behavior in a complicated manner. Their impacts and interrelationships are investigated using genetics, physiology, epidemiology, and other disciplines.

Section of Healthy Longevity Researches

In collaboration with local municipalities, community residents, academic institutions, national research organizations, industry, and other stakeholders, research are ongoing to identify the causes of frailty and sarcopenia, and their potential interventions. These scientific evidence for extending healthy life expectancy will be applied to real world.

Section of Energy Metabolism

This section measures average daily energy expenditure using the doubly labeled water method, human calorimetry, and other techniques, and contributes to the determination of the estimated energy requirements in the *Dietary Reference Intakes for Japanese*.

International Research Collaboration and Partnership

Section of International Nutrition Strategy

This section promotes collaboration with the WHO and other international organizations. It also coordinates joint research projects with health or nutrition research institutions in Asian-Pacific countries. The Section also oversees a program for international cooperation that invites foreign researchers to Japan every year and it holds an international symposium every other year.

Section of Population Health Metrics

To support the development and assessment of public health policies aimed at preventing lifestyle-related diseases, our efforts encompass: (1) conducting research on health metrics by analyzing survey data sourced from official statistics, (2) performing economic evaluations on sustainable and healthy diets, and (3) fostering international cooperation to compile comprehensive global health statistics.

Section of Global Disaster Nutrition

This section collects the knowledge and experience of people living in this disaster-prone country, and disseminates them to national and international stakeholders. To prevent post-disaster health damage, it works to solve the food- and nutrition-related problems experienced by disaster-affected people and to fill gaps in their nutrition. It also provides evidence-based logistical support.

Section of Research Collaboration and Partnership

In order to realize a healthy and delicious diet that can be continued naturally, we are implementing the Industry-Academia-Government Joint Research Project to Promote the Improvement of the Food Environment together with food companies. We aim to build a food environment model in which all people, not just those who are highly health conscious, can naturally achieve good health.

Promotion of Pharmaceutical Development

Promoting the Development of New Medicines and Medical Devices

In order to effectively promote the development of pharmaceuticals, medical devices and cellular and tissue-based products, we collaborate with universities, companies, and research institutes in accordance with the stage of development, and we draw on our expertise to provide guidance and advice so that pharmaceuticals and other products can be commercially viable.

Promoting the Development of Orphan and "Specific-Use" Medical Products

The NIBIOHN provides financial support, guidance, and advice to accelerate the development of products that have been granted the orphan or "specific use" medical products designation by the Minister of Health, Labour and Welfare.

Development Support: Specialized Program

The NIBIOHN provides guidance and advice to support startups, small businesses, and other enterprises involved in the final stages of clinical development. Specifically, current activities center around the "projects suited for practical application" of medicine and medical devices that received national funding between FY 2004 and FY 2010.

Administration of the Fund Supporting Domestic Production of Antibiotic APIs

In order to ensure a stable supply of antimicrobial substance preparations, we provide subsidies and carry out related operations to fund the efforts of certified supply providers to secure antimicrobial substances in accordance with the Certified Supply Assurance Plan for Antimicrobial Substance Preparations stipulated in the Enforcement Order of the Economic Security Promotion Act.