

HEALTHY LONGEVITY GLOBAL COMPETITION

2024 Catalyst Awardees

Sponsor: Agency for Medical Research and Development of Japan

Aiming for Vascular Regeneration and Rejuvenation Using iPSC-3D Vasculature

Principal Investigator	TOYOHARA Takafumi, MD PhD
PI Primary Affiliation	Tohoku University Hospital
Co-Investigator(s)	ITAI Shun, PhD

PROJECT DESCRIPTION

Atherosclerosis, the leading cause of stenosis and occlusion in major arteries, results in life-threatening ischemic conditions such as coronary artery disease and stroke. Current treatments, including vascular interventions and bypass surgery, often encounter restenosis—a recurrence of artery narrowing—highlighting the urgent need for more effective therapies.

Our groundbreaking approach leverages regenerative medicine, replacing damaged blood vessels with new, healthy ones. We have pioneered a revolutionary therapy using 3D blood vessels created from human induced pluripotent stem cells (iPSCs). These iPSC-derived vessels are not only structurally similar to human blood vessels but also function comparably—a world-first achievement. The use of iPSCs offers significant advantages: they provide an unlimited and reliable source of vascular cells and have the potential to bypass immune rejection, both essential for clinical applications.

Our innovative therapy targets a broad range of conditions, including atherosclerosis-related diseases, synthetic organ generation and transplantation, and congenital heart disease. Initially, our focus will be on Lower Extremity Arterial Disease (LEAD), a severe condition where the major arteries in the legs become narrowed or blocked. LEAD can cause ulcers, gangrene, and increase the risk of amputation, significantly diminishing quality of life. Unmet medical needs are particularly high for LEAD compared to other atherosclerotic diseases.

Our minimum viable product has been tested in small animals and we will use Catalyst funding to advance to large animal testing prior to clinical application. This breakthrough therapy has the potential to dramatically improve quality of life and promote healthy aging on a global scale.

Analysis of Bowel Sound Big Data and Development of an Application for the Prevention of Bowel Diseases

Principal Investigator	KANEGAWA Norimasa
PI Primary Affiliation	Suntory Global Innovation Center Ltd.
Co-Investigator(s)	None

PROJECT DESCRIPTION

"GutNote (Chonote)" Health App: Bowel Sound Analysis and Behavior Modification

Our app, "GutNote," utilizes smartphone capabilities to collect and analyze often overlooked data: bowel sounds. Through a unique deep learning model, we have developed a distinctive and popular health app.

By accessing and analyzing this extensive bowel sound data, our objective is to contribute to the prevention and early detection of intestinal-related diseases like chronic constipation and irritable bowel syndrome. Chronic constipation, especially prevalent among older individuals, significantly affects their quality of life. Therefore, our aim is to enhance the health and longevity of older users by preventing this condition.

Moreover, individuals suffering from constipation often underestimate the severity of their condition, foregoing hospital visits, which can result in worsening symptoms. To address this, we provide support through a user-friendly app that serves as a convenient self-awareness tool, helping individuals gain a better understanding of their own condition.

Our app utilizes smartphones to measure physiological sounds and incorporates the NUDGE theory to drive behavior modification. With optimized UI/UX, it categorizes gut types and visualizes gut conditions with a score. Our goal is to cultivate healthy habits by starting with bowel sound measurement and promote user engagement in managing their health. By exploring the untapped potential of bowel sound analysis, we strive to establish a new era of personalized health habits, empowering users to track and improve their health behaviors.

Biomarker-linked nucleic acid medicines for heart failure

Principal Investigator	KOMURO Issei, PhD, MD
PI Primary Affiliation	The University of Tokyo Graduate School of Medicine
Co-Investigator(s)	NOMURA Seitaro, PhD, MD NAITO Mitsuru, PhD KIMURA Yasuaki, PhD YOSHIOKA Kotaro, PhD, MD

PROJECT DESCRIPTION

The heart pumps blood throughout the body, but pathological stresses such as high blood pressure or myocardial infarction can impair its function, leading to heart failure. The incidence of heart failure is rapidly increasing, primarily due to an aging population, resulting in a global heart failure pandemic. Currently, approximately 64 million people worldwide suffer from heart failure and face life-threatening risks.

We pioneered the cardiac single-cell RNA-seq analysis to explore heart failure pathology in mice and humans. Our research highlighted DNA damage in cardiomyocytes as crucial (Nature Communications. 2018; Nature Cardiovasc Res. 2022; Science Adv. 2023; Circulation. 2024) and identified IGFBP7, secreted by damaged cardiomyocytes, as a key marker of severe heart failure (Nature Communications. 2022). We demonstrated that targeting IGFBP7 in the cardiac microenvironment is an effective treatment (Circulation. 2024). Additionally, we clarified heart failure-specific transcriptional mechanisms through single-cell multi-omics analysis and developed gene therapies targeting these mechanisms. We further developed a drug delivery system (DDS) with cardiac-specific ligands, without the need for adeno-associated virus vectors, while advancing nucleic acid technologies for improved gene suppression.

In this study, we aim to develop a new nucleic acid drug for heart failure that targets transcriptional regulation and the microenvironment in the heart. By combining heart failure-targeting molecules, drug delivery systems, and nucleic acid technologies, we seek to create the first drug addressing the molecular mechanisms of heart failure. This breakthrough aims to address a major health threat to the elderly and promote healthy longevity.

Development and clinical application of Ostrich-derived Freeze-Drying Small Diameter Decellularized Vascular Graft

Principal Investigator	MAHARA Atsushi, PhD
PI Primary Affiliation	National Cerebral and Cardiovascular Center Research Institute

Co-Investigator(s)	YAMAOKA Tetsuji, PhD YAMANAKA Hiroki, PhD, MD MORIMOTO Naoki, PhD, MD IDE Junichi, MS
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PROJECT DESCRIPTION

Artificial vascular grafts made of polymeric materials with the inner diameter of 6 mm or larger are used daily in the surgical treatment of vascular diseases and have saved the lives of many patients. In contrast, small-diameter vascular grafts with the inner diameter of 4 mm or less have not been satisfactory for practical use, despite a history of research and development of more than half a century. Our research group focused on the carotid arteries of the ostrich. They provide decellularized small-diameter artificial blood vessels with good mechanical properties and a shape (inner diameter 2-4 mm, length 60 cm) that can withstand actual clinical use by immobilizing antithrombotic and endothelialization-inducing peptides. Furthermore, as a breakthrough technology for practical use, a special drying process has been established which allows them to be provided to medical institutions at room temperature like conventional synthetic vascular grafts.

The first target of this world's first artificial vascular graft is to avoid lower limb amputation by adapting it to severe lower limb ischemia. It can also be adapted to coronary artery bypass for elderly people and will solve issues directly related to postoperative health and happiness. We have developed a new drying process that preserves the collagen structure of decellularized blood vessels by alcohol treatment. We will evaluate the collagen structure by X-ray structural analysis and assess the structure and performance by preclinical transplantation experiments using miniature pigs, aiming to commercialize the world's first xenogeneic small-diameter artificial blood vessel.

Development of a Health Promotion Program for the Integrating Food and Oral Health Education with Digital Health for Older Adults

Principal Investigator	MATSUO Koichiro, DDS, PhD
PI Primary Affiliation	Tokyo Medical and Dental University ----> New affiliation after 10/1 Institute of Science Tokyo
Co-Investigator(s)	MASUDA Yuji, DDS, PhD

PROJECT DESCRIPTION

Innovative Concept:

The comprehensive awareness modification of mouth, chewing and meal (CAMCAM) program is an innovative initiative that integrates oral health, chewing, and nutrition education. It offers participants textured "CAMCAM" lunches, coupled with lessons on oral health and nutrition. This innovative program integrates digital health, using user-friendly SNS apps, connecting both online and offline communities. This ecosystem promotes continuous health behavioral change through social connections.

Contribution to Healthy Longevity:

The program adopts a comprehensive approach to oral and nutritional health, raising participants' awareness and reducing risks of malnutrition, obesity, and frailty, thereby extending healthy lifespans. Through the program and continuous follow-up via SNS apps, participants experience the joy of eating.

Impact on Elderly Health and Happiness:

The program is expected to have multifaceted impacts on elderly health and happiness:

- Sustained behavioral changes in oral and general health, reducing risks of lifestyle diseases and frailty.
- Strengthened social connections through SNS app communities, reducing isolation.

- Social impact through sustainable projects, contributing to reduced social security costs and community health promotion.

Plan Design:

The plan involves a six-month program where participants receive monthly "CAMCAM" lunches, lectures on oral health and nutrition, and regular updates via an app. The app evaluates frailty, oral health, and behavioral changes. High-risk identification and individual consulting are also conducted.

Implementation Plan:

This program can extend healthy lifespans by solving oral and nutritional challenges. It targets all age groups, from children to older adults, and can be implemented through collaborations with municipalities, care providers, and schools, making it suitable for nationwide implementation.

Development of a hybrid nano-coated nitinol drug-eluting stent (Hybrid-DES) for small atherosclerotic lesions in below-the-knee (BTK)

Principal Investigator	HASEBE Terumitsu, MD, PhD
PI Primary Affiliation	Tokai University School of Medicine
Co-Investigator(s)	MAEGAWA Shunto, PhD, MBA OKAMOTO Yutaka, MEng HOSAKA Makoto, MEng EDELMAN R. Elazer, MD, PhD, FACC

PROJECT DESCRIPTION

Arteriosclerosis obliterans (ASO) causes arterial occlusion in the lower extremities, with risk factors like diabetes, smoking, aging, hypertension, dyslipidemia, and renal failure. In severe cases, the one-year prognosis includes a 30% risk of lower limb amputation and a 25% risk of death. ASO affects over 230 million adults worldwide, and amputation significantly impacts mobility, mental health, and increases the need for social and medical support.

Treatment options include surgical bypass and endovascular procedures like catheterization. While above-the-knee treatments have advanced, below-the-knee (BTK) device development faces challenges like smaller vessels, slower blood flow, and high calcification. The standard BTK treatment, balloon catheter dilation, often results in a 70% restenosis rate within three months, requiring repeated interventions.

Our team has developed a novel drug-eluting stent to maintain long-term patency in BTK cases. Since 2000, we have focused on the antithrombotic and biocompatible properties of fluorine-doped diamond-like carbon (F-DLC) nanocoating. This has been applied to NiTi stents with an active polymer coating to inhibit reactions to foreign materials, which accelerates vascular healing.

This hybrid stent has shown promising preclinical results, maintaining patency for up to six months. Supported by AMED, we have developed both the hybrid stent and its delivery system, with plans for clinical trials aiming for regulatory approval in Japan by 2028. We also intend to expand internationally through joint trials in Japan and the U.S. This stent aims to achieve a restenosis rate of 30% after 12 months, improve patient 5-year survival rates, preserve mobility, and reduce associated disease risks.

Development of mRNA mediated expression method in peripheral blood to engineer obesity-resistant immune cells

Principal Investigator	TODA Gotaro, MD, PhD
PI Primary Affiliation	The University of Tokyo

Co-Investigator(s)	None
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PROJECT DESCRIPTION

Obesity is a major risk for the development of diabetes, kidney and heart disease, and musculoskeletal disorders, each of which diminishes quality of life. Although inflammation has been extensively reported in the development of obesity, immune cells have also been shown to sustain normal metabolic function, such as energy production and storage, and maintaining normal body weight, which are dysregulated in obesity. These normal processes are diminished in age related inflammatory states (referred to as “inflammaging”) as well. We have previously reported that production of the cytokine IL-10 is dysregulated in obesity, resulting in aggravated gluconeogenesis and elevated glucose levels after eating (Toda G et al. Mol Cell. 2020). This project aims to identify potential pathways that maintain the normal function of immune cells, and to engineer obesity-resistant immune cells from peripheral blood that can be returned to the blood flow to improve pathological changes in obesity. We will search for target factors among genes that are increased/decreased by short-chain fatty acids (SCFAs), which have been shown to protect against obesity. We will merge spatial transcriptomics data of adipose and renal tissue from patients with or without obesity to identify targets with clinical potential, focusing on protein degradation, which was heightened under SCFA treatment in preliminary experiments. mRNA therapeutics will be key in introducing the relevant factor and in collecting cells that have obesity-resistance. We hope cell-based methods to maintain normal immune function may in the future be utilized in other immune dysregulating conditions, including age related disorders.

Development of novel heart valve therapy using autologous tissue-engineered artificial heart valve

Principal Investigator	SATO Yasushi, PhD.
PI Primary Affiliation	Asahikawa Medical University
Co-Investigator(s)	TAKEWA Yoshiaki, MD, PhD. INOUE Yusuke, PhD. TERAZAWA Takeshi, PhD.

PROJECT DESCRIPTION

Valvular heart disease is caused by congenital malformations or age-related tissue degeneration. Approximately 200 million patients worldwide are estimated to suffer from valvular diseases, and this number is expected to rise with the aging population. One treatment for severe cases is valve replacement surgery using artificial valves. However, current artificial valves, such as mechanical and bioprosthetic valves, have limitations in antithrombotic properties and durability, leading to a significant burden on patients.

Biovalve represents a groundbreaking advancement in heart valve therapy, offering substantial benefits for both elderly and pediatric patients. Unlike conventional artificial valves, which require lifelong medication and have limited durability, Biovalve is created entirely from the patient's tissue by simply subcutaneously implanting a mold. This method harnesses the body's natural healing abilities to produce a personalized heart valve, avoiding risks such as immune rejection and toxicity.

For pediatric patients, Biovalve's ability to grow and adapt with the child significantly reduces the need for multiple surgeries as they age. Similarly, for older patients, Biovalve's durability and superior antithrombotic properties minimize the need for re-operations and hospital visits, enhancing quality of life and independence. By reducing ongoing medical interventions and associated risks, Biovalve promotes healthier, longer lives for patients of all ages. Research in large animals is underway to optimize the design and evaluate its function, with clinical trials planned once safety and efficacy are confirmed. Our goal is to validate Biovalve's safety and effectiveness and bring this innovative solution to patients worldwide, ultimately transforming heart valve therapy.

Development of tailor-made behavior change programs based on prediction of future cognitive function

Principal Investigator	MIMURA Masaru, MD, PhD
PI Primary Affiliation	Keio University
Co-Investigator(s)	KISHIMOTO Taishiro, MD, PhD SHIMIZU-HIROTA Ryoko, MD, PhD HORIGOME Toshiro, MD, PhD FURUKAWA Shota, MD NAKAI Fumiya, MSc

PROJECT DESCRIPTION

As Japan is a superaged country, enhancing the cognitive reserve of the elderly is crucial. However, conventional disease education, which recommends healthy lifestyle habits such as exercise and diabetes prevention, has faced the challenge of low adherence due to unclear individual outcomes. Our suggested approach thrives to address these challenges by developing a prediction software that visualizes future individual cognitive functions based on daily activities.

Keio University Center for Preventive Medicine has accumulated annual health checkup data. In addition, data from cohort studies conducted at the university have also been accumulated. Using this data, we are trying to develop software that uses machine learning to estimate cognitive function five years by entering current cognitive function and lifestyle habits. In addition, by using counterfactual, the software can suggest individualized behavioral changes to see what lifestyle changes would be useful to prevent cognitive function decline. The above program is being developed as an industry-academia collaborative project between Keio University and Hitachi. We are also developing a tool with Splink to enable the elderly to perform cognitive training at home at any time using their smartphones.

By using these programs, elderly people can see the risk of cognitive decline as their own and make the behavioral changes that are best for them to prevent cognitive decline. They will also be able to incorporate simple cognitive training tools into their daily lives.

Keio University plans to demonstrate the effectiveness of these software programs in clinical studies and aims for early social implementation with participating companies.

Exercise prescription system using an internet of things (IoT) for medical treatment: verifying effects from genetic to clinical levels

Principal Investigator	MASUKI Shizue, PhD
PI Primary Affiliation	Shinshu University Graduate School of Medicine
Co-Investigator(s)	NOSE Hiroshi, MD, PhD

PROJECT DESCRIPTION

We developed an exercise prescription system using the IoT, which enables individuals to receive instructions for performing interval walking training (IWT) according to their physical fitness from a central server. Using the system, we examined the effects of IWT in 10,000 middle-aged and older people and reported that 5-month IWT increased physical fitness by ~15%, improved symptoms of lifestyle-related diseases by ~20% and other age-associated diseases by ~30%, and decreased healthcare costs by ~20% (Compr Physiol 10: 1207-1240, 2020). As for the mechanisms, while mitochondrial dysfunction due to sarcopenia with aging reportedly causes chronic systemic inflammation, we found that IWT suppressed pro-inflammatory gene expression with increased physical fitness. In other words, the seemingly diverse symptoms of the diseases are fundamentally caused by chronic inflammation and can be improved if physical fitness is increased by IWT.

Accordingly, we plan to examine the effects of IWT on diseases, from genetic to clinical levels, in “patients” who regularly visit hospitals. To do this, we recently launched the “Sports Medicine Clinical Research Center” at Shinshu University School of Medicine, where we will accumulate evidence of the effects of IWT on diseases in cooperation with clinical staff. Once collected, this evidence would enable us to change the current drug/organ specific medical system into a non-drug/integrative one, thereby reducing healthcare costs. Subsequently, we hope to spread this system to regional core hospitals throughout the country and build a healthy longevity society by activating the health service industry through reduced healthcare costs.

Float-Ring Implant: Development of a Cushioning Device to Suppress Knee Osteoarthritis After Meniscal Tears

Principal Investigator	YAMAKO Go, PhD
PI Primary Affiliation	University of Miyazaki
Co-Investigator(s)	CHOSA Etsuo, MD, PhD

PROJECT DESCRIPTION

A super-aging society must transition into a “healthy and longevity society” by addressing challenges related to bones, joints, and the musculoskeletal system. Osteoarthritis, a degenerative joint disease, causes pain, swelling, and stiffness, leading to restricted mobility. With aging populations, rising obesity, and increased injuries, the prevalence of osteoarthritis is expected to grow globally. However, effective treatments to prevent knee osteoarthritis are lacking, particularly after significant meniscal damage. We have developed the “float-ring”, an innovative implant designed to act as a cushion following partial or total meniscectomy, aiming to reduce knee pain and slow osteoarthritis progression. The meniscus, a fibrous cartilage, plays a vital role in load distribution and joint stability. When damaged, healing is limited to areas with blood supply, and sutures often result in unsatisfactory outcomes due to retears. In cases where suturing is not feasible, meniscal resection is performed, which can exacerbate cartilage damage and accelerate osteoarthritis. The float-ring is a non-absorbable, flexible implant that conforms to the joint surface during knee movement, reducing cartilage stress through effective load distribution. We believe that once fully developed, this implant will be a key innovation in promoting healthy longevity.