National Cerebral and Cardiovascular Center **Research Institute & Open Innovation Center**

To understand the mechanisms underlying cardiovascular diseases and to develop new therapies and diagnosis methods



Remarks at the Opening of New Research Institute (RI) and Open Innovation Center (OIC)

Director General of RI Naoki Mochizuki

Since 1977 when the old research institute was established, we performed a variety of fields of cardiovascular research for prevention, suppression, and treatment of cardiovascular diseases. Our mission has been "Contribution to the happiness of people by curing cardiovascular diseases".

We moved to KENTO (K:knowledge, E: Exercise, N: Nutrition, To: Town) from Fujishirodai in Suita city on July 1st of 2019 and started to work in the new research institute. By refreshing the working circumstances of research, we again decide to continue our research to fight cardiovascular diseases that restrict the quality of lives. We face the problem with aging society and need to improve the quality of patients with cardiovascular diseases. Therefore, we need to decrease the number of the patients by developing new methods for prevention, diagnosis, and treatment. Now we feel that we should reconsider how we perform innovation in our research field by completely resetting our way of thinking or by reestablishing new strategies based our accumulated knowledge and experience.

We hope that we here assemble not only researchers but also knowledge and data stored until now. We do our best as researchers who have the privilege to work here in the one of National Centers supported by the ministry of Health, Labour and Welfare.

Director of OIC Yoshihiro Miyamoto

To realize next-generation medical care / healthcare, open innovation that utilizes resources spread around the world is becoming essential. In Japan, however, it is essential to establish a facility where knowledgeable people gather because the mobility of researchers is extremely low. Therefore, the new NCVC has established the Open Innovation Center (OIC) and a system where necessary knowledge is gathered and original resources are utilized.

Specifically, the Department of Industrial-Academic Collaboration has been newly established within OIC to strongly promote industrial-academic collaboration. In addition, the Biobank, the Department of Medical and Health Information Management, and the Omics Research Center have been incorporated into the OIC as R & D sites utilizing bioresources and clinical data. The Training Center in the Department of Promotion of Education with advanced treatment equipment for internal staff training can also be used by external researchers.

We have also established Open Innovation Laboratory (OIL) for joint research with companies and universities "under one roof". In addition, the Science Café will offer activities such as seminars that promote the interaction between researchers. Through these activities, we would like to realize innovative medical care and medical technology through open innovation.

6F 3F **Open Innovation Center (OIC) Research Institute** 61213 Seminar Room 305 605 Biobank Dept. Cell Biology 604 304 ŶŶ. Dept. Molecular Pharmacology **Open Innovation Laboratory** 台 彭 601 603 303 Dept. Bioscience and Genetics Open Innovation Laboratory Dept. Biochemistry 602 302 Dept. Molecular Physiology Open Innovation Laboratory 2F **5F** Open Innovation Center (OIC) **Research Institute** 507 Dept. Preventive Medicine and Epidemiology 505 **Research Institute** Dept. Vascular Physiology 206 506 ¢1 Dept. Medical and Health Information Management 207 韻 些 501 503 504 91 Dept. Molecular Innovation in Lipidology Dept. Molecular Pathogenesis Dept. Genomic Medicine 盐 502 51203 Dept. Cardiac Physiology Seminar Room 4F 204 211 Promotion of Education • Training Center Large/Middle Conference Room 406 **Research Institute** Dept Bio-Medical Imaging 405 205 **Director General of OIC** Dept. Research Promotion and Management Deputy Director of OIC 藟 407 404 Administration Dept. Biomedical Engineering 巤 Science Cafe 彭 401 Seminar Room 1F-B1 403 Dept. Artificial Organs Dept. Regenerative Medicine and Tissue Engineering

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Seminar Room

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Large Conference Room

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Dept. Cardiovascular Dynamics

Animal Center

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Open Innovation Laboratory

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Dept. Industrial-Academic Collaboration

Dept. Research Ethics and Bioethics

Omics Research Center

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Research Institute ——	Dept. Bioscience and Genetics Dept. Molecular Physiology Dept. Biochemistry Dept. Molecular Pharmacology Dept. Cell Biology	Area 601 602 603 604 605
	 Dept. Molecular Pathogenesis Dept. Cardiac Physiology Dept. Molecular Innovation in Lipidology Dept. Genomic Medicine Dept. Vascular Physiology 	501 502 503 504 505
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	Dept. Preventive Medicine and Epidemiology Dept. Research Promotion and Management Dept. Research Ethics and Bioethics	507 405 · 406 203
Open Innovation Center —	Omics Research Center Biobank Dept. Industrial-Academic Collaboration Promotion of Education • Training Center Dept. Medical and Health Information Management	301 305 201 204 206

Dept. Bioscience and Genetics

Understanding the Genetic Background of Cardiovascular Diseases

We have tried to understand the genetic background of cardiovascular diseases. Inherited primary arrhythmia syndromes and idiopathic cardiomyopathies are ones of the major inherited cardiovascular diseases. We perform genetic analysis of the patients, find causative gene mutations and search for the mechanisms of the diseases. In common cardiovascular diseases, we analyze the single nucleotide polymorphisms which affect the onset and prognosis of the diseases. Thorough these studies, we aim to realize precision medicine, a medical care based on the personal genetic background. In addition, we use the genome editing technology CRISPR-Cas9 system and support creating animal models for the research.



• Structural variant detected by Nanopore, Gridlon, a long-read sequencer Genome editing technology using CRISPR-Cas9 system

Dept. Molecular Physiology

Signal Transduction in Development and Disease

We study the mechanisms of cardiovascular development, focusing on signaling pathways implicated in human diseases and their downstream target genes such as those encoding transcription factors, transmembrane proteins and protein kinases. While mainly utilizing animal models in our experiments, we are especially interested in basic research that is ultimately informative and translatable to the diagnosis and treatment of congenital or adult-onset cardiovascular diseases. We are also dedicated to education and training to pass the intellectual richness and professional strengths of our research center on to biomedical scientists and physician-scientists of the next generation.

- Cutting-edge technologies to create genetically-modified animal models for human diseases
- Modern "omics" approaches for cellular signal transduction studies and clinical application







Dept. Biochemistry

Discovery of Novel Biologically Active Peptides

We have been investigating biologically active peptides, which take on important roles for maintaining homeostasis in the cardiovascular and metabolic systems, to elucidate their functions and physiological significance. Our goal is the reconstruction of the signal transduction network in the cardiovascular system on the molecular basis. Furthermore, we are aiming to introduce these biologically active peptides into clinical application.

- Our lab focuses on the discovery of novel biologically active peptides and on the search for their functions
- We are aiming to introduce these peptides into clinical application



Dept. Molecular Pharmacology

Drug Discovery Satisfying Unmet Medical Needs in the Cardiovascular Field

Protein structure is all but a function, and is a key to create complexity of human biology. Abnormality of protein structure causes human diseases. To tackle unmet medical needs in cardiovascular field, we need to identify a key molecule and understand its protein structure. In addition to structural analysis, we have established our own assay system and disease model. Our main target areas are: (i) Mitochondrial energy production, (ii) Cerebral aneurysm and local inflammation.

- High-throughput screening of chemical compounds that can modulate OXPHOS (oxidative phosphorylation) activity.
- Target identification based on the protein structure in combination with in-silico screening
- Structure-based drug development (SBDD)
- A unique animal model for spontaneous rupture of cerebral aneurysm, which will be used for understanding pathogenesis and drug development



Identification of binding sites for the hit compounds by co-crystallography



Dept. Cell Biology

Understanding the Development and Impairment of Circulatory System

We have tried to understand the molecular mechanisms by which the cardiovascular system (circulation) is established in zebrafish embryos and to decipher how circulatory system is worsening with age. Circulation is an essential system that precedes other organ development to deliver appropriate oxygen and nutrition. Once circulation is impaired, organs are less oxygenated and nourished, thereby being damaged reversibly or irreversibly. Genetic control for establishment of circulation and exposome that affects living creatures are conserved in the vertebrates and zebrafish. Therefore, by understanding the mechanisms underlying development and impairment with ageing, we investigate the general mechanism for rebuilding the circulation including angiogenesis and cardiogenesis and for preventing circulatory system from deterioration with age. Our basic method is simultaneous visualization of signal transduction as well as morphology of organs/tissues.

- Unique approach using zebrafish (developing signal transduction-monitoring zebrafish)
- Collaboration with pharmaceutical companies to develop new drugs for cardiovascular system and ageing





Monitoring BMP signal activation (left), Visualization of bloods (Center), and Ca²⁺ signaling (right) of beating heart

Dept. Molecular Pathogenesis

Hemostasis and Thrombosis

Blood is required to have opposing functions; continuous fluidity and rapid clotting. Altered balance between fluidity and clotting can lead to bleeding or thrombogenesis. In order to overcome cardiovascular diseases related to hemorrhage and thrombosis, we are conducting research on plasma proteins, platelets, vascular endothelial cells with a wide variety of approaches from the molecular to the physiological level. We are also focusing on putting the results of basic research into clinical medicine, such as the development of new diagnostic methods.

- One of the few laboratories in Japan that studies blood coagulation from the perspective of basic biology
- Genetic analysis of patients with abnormal blood coagulation and functional analysis of genetic abnormalities
- Development of new assay methods that lead to practical use in clinical settings
- Analysis of mice lacking proteins involved in endoplasmic reticulum-associated degradation





Cell analysis



Animal analysis



New assays

Dept. Cardiac Physiology

Pathophysiology of Cardiometabolic Disease

Prolonged insulin resistance results in adverse and even irreversible effects on all cells of the heart and interdependent lungs and kidneys. Our research aims to understand common and unique mechanism of metabolic dysregulation that drive cardiopulmonary and renal dysfunction over the life course in settings of hypertension, obesity, premature ageing and cardiomyopathies. We also investigate if novel therapies and regular exercise training can prevent the onset or even reverse metabolic heart disease. Our research incorporates many state-of-the-art techniques including synchrotron imaging and omics analyses to investigate disease from the whole organism to cell and molecular levels.

- Identifying the molecular basis of microvascular endothelial dysfunction with microangiography
- Integrated cardiovascular physiology assessment with PV loop analyses, microdialysis, telemetry and sympathetic nerve recording techniques
- Drug characterization pipeline from in vivo animal studies to in vitro analysis







1,1 Reflection (Actin-Myosin)



Area 503 Dept. Molecular Innovation in Lipidology

Development of New Therapies for Dyslipidemia and Atherosclerosis

We have been studying the mechanisms of dyslipidemia and atherosclerosis. Our goal is to develop new drugs for prevention and treatment of atherosclerosis based on our lipid research.

- Genetic analysis for clarifying etiology and pathophysiology of dyslipidemia
- Development of antisense drugs targeting dyslipidemia
- Making guidelines of familial hypercholesterolemia
- Development of a novel therapy for atherosclerosis based on the evaluation of quality and quantity of HDL



Dept. Genomic Medicine

Understanding Genetic Architecture of Cardiovascular Diseases

We aim to realize precision medicine based on individual genetic information. Genetic factor is a risk for cardiovascular disease. We analyze the whole genome data of humans by statistical genetics, statistics, and bioinformatics to identify the causative genes of diseases and construct the prediction model. We reveal the mechanisms of cardiovascular diseases not only by the genome but also by omics information such as the metabolome.

- Genomic study of cardiovascular diseases by whole genome analysis of human
- Revealing the mechanisms of cardiovascular diseases with statistical genetics, statistics and bioinformatics





Whole genome analysis for Next Generation Sequence

Dept. Vascular Physiology

Understanding the Molecular Mechanism of Vascular Diseases

We are interested in the molecular mechanisms of intractable vascular diseases such as pulmonary arterial hypertension (PAH) and large vessel vasculitis (LVV). We have been focusing on the involvement of "inflammatory cytokines" and "transcriptional factors" in the pathogenesis of PAH and LVV. Our goal is to develop novel diagnostic methods and therapeutic modalities for intractable vascular diseases.

- Integrative and comprehensive research to elucidate the molecular mechanisms of vascular diseases using samples of both human patients and disease animal models
- Successful development of a novel therapeutic strategy (anti-IL-6 receptor antibody tocilizumab) for TAK
- Elucidating novel molecular culprits for the pathogenesis of pulmonary arterial hypertension (PAH)
- Elucidating the molecular mechanism connecting vasculature and hematopoiesis



Vascular lesions and right ventricular systolic pressure of a severe PAH model rat



FACS analysis of murine immune cells



Vascular structure of mouse bone marrow



Metagenome analysis of the patients with an intractable vascular disease

Dept. Artificial Organs

Development of Mechanical Circulatory Support Systems

Department of Artificial Organs has dedicated to the development of medical devices to treat severe cardiac/respiratory failure, including an ECMO system and ventricular assist devices (VAD) and studies on the effect of such devices on patients and control strategy for them. Currently, several device development projects are going on under collaboration with industries. We are also developing testing facilities for human engineering studies to improve the quality of medical therapies using these devices.



Dept. Cardiovascular Dynamics

Clinically-Oriented Understanding of and Intervention in Hemodynamics

Our aim is to optimize, improve, and refine the treatment of cardiovascular diseases in clinical practice. We are conducting the 3 steps research.

- The research for modelling the functions of the cardiovascular system
- The research for integrating and regulating the cardiovascular system
- The development of medical devices to artificially intervene in the cardiovascular system, and the evaluation of various medical devices by precise physiological measurements (the joint research with companies)



Dept. Regenerative Medicine and Area 403 Tissue Engineering

Understanding Mechanisms of Cardiac Regeneration

The capacity for regeneration is extremely limited in mammals, contributing to mortality and morbidity from a host of diseases. Our work focuses on molecular and cellular regulations that are retained in certain animals to control full regeneration of complex structures like the heart, but may be silenced or lost in mammals during evolution. We propose that major therapeutic advances can be made by understanding the mechanism of natural regeneration in zebrafish, a genetically tractable model possessing a spectacular capacity for regeneration, and that fish-like regeneration can be induced in humans to treat cardiovascular diseases.

- Using genetic approaches to visualize gene expression and cell populations or manipulate gene function in adult zebrafish to understand endogenous mechanisms of heart regeneration
- Using both regenerative zebrafish and non-regenerative adult mouse models to understand how roadblocks to regeneration can be removed in human hearts



Klf1-induced cardiomyocyte renewal





Transcription factor network regulated by Klf1

Dept. Biomedical Engineering

Research and Development of Emerging Medical Devices

Our research team is composed of multidisciplinary specialists in material science, mechanical engineering, cell engineering, tissue response, immune system, animal experiments, and clinical research. We have been focusing on the research and development of novel medical devices such as small-diameter blood vessels [A] and heart valves [B] in collaboration with universities and companies. Recently our research area has been inevitably extended to tissue engineering/regenerative medicine [C], stem cell-based therapy [D], novel drug discovery [E], and imaging agents [F].

- Small-diameter acellular long bypass with established POC is testing its safety to proceed towards a clinical trial.
- Clinical tests of high hydrostatic pressure instruments [C] which can completely kill skin cancer cells are ongoing.



Dept. Advanced Medical Technologies

Preclinical and Basic Research Using 7T-MRI

The Department of Bio-Medical Imaging has been developing methodological tools for image-based diagnosis, using 7T magnetic Resonance Imaging (MRI). A new imaging and image processing theory has been established for the quantitative in vivo assessment of several biological and physiological functions. We are also aiming at applying these methodologies to investigate the pathophysiology of ischemic diseases both in the brain and the heart using preclinical 7T-MRI. Recent research topics from our group are presented in the following.

- Evaluation of cerebral and cardiovascular disease models using ultra-high field 7T-MRI
- Development of new imaging technology using ultra-high field 7T-MRI









Area 406

Dept. Preventive Medicine Area 507 and Epidemiology

Research of Big Data and Artificial Intelligence Analyses

The mortality rate due to cardiovascular disease (CVD) has declined in Japan. However, the incidence of CVD has been increasing in recent years with aging. To develop and promote a strategy for CVD, it is essential to identify risk factors for CVD. In our department, we aim to conduct epidemiological research and information science research on artificial intelligence for DVD to accumulate knowledge that contributes to the improvement of healthy life expectancy.

- Data mining by using natural language processing such as IBM Watson for electronic medical records (participating in projects for AI Hospital, supported by the Cabinet Office)
- Predicting outcomes for CVD by using machine learning and deep learning, and applying AI to diagnostic imaging of aneurysm and vulnerable plaques (Philips-NCVC Project)
- Research using nationwide CVD database such as J-ASPECT study, JROAD study, and All Japan Utstein Registry
- Development of the predictive model for heat stroke based on data for the 10 million population in the Kansai area (Environment Research and Technology Development Fund of the Ministry of the Environment)
- Development of monitoring technology for patients with dementia using AI-powered disaggregation technology (Funded by Tokyo Electric Power Company)



Dept. Research Promotion Area 405, 406 and Management

Research Promotion and Research Integrity

The animal experiment labs have animal holding areas and advanced facilities intended for large experimental animals to develop clinical research. We believe favorable rearing environments for animals contributes to experimental results with high reliability and reproducibility. We pay close attention to preventing the spread of infectious diseases.

- Animal holding rooms accommodating large animal pairs
- Individually ventilated cages





Dept. Research Ethics and Bioethics

Resolving Ethical Issues Arising in Clinical Research and Practice

To promote ethics in medicine, we conduct research as well as provide education and consultation services on various ethical issues arising with the advancement of clinical research and practice. We adopt both theoretical and empirical research methods for analyzing problems. The targets of our training programs and consultation service are clinical researchers, ethics committee members, healthcare professionals, and younger consultants within and external to the NCVC.

- Research on the ethical, legal, social and policy issues in clinical research, e.g., clinical trials, bio-banking, informed consent, and research integrity
- Research on clinical ethics and bioethics
- Ethics training and consultation service



Number of Ethics Consultation Requests

Omics Research Center

To Decipher Unexplored Molecular Basis of Cardiovascular Diseases by Means of Multi-Omics Approaches

Identification of novel biological, genetic, and clinical markers is essential for the "Precision Medicine" that achieves early diagnosis and prevention of patients at risk. By implementing multi-omics approaches including comprehensive genetic, genomic, proteomic, transcriptomic, and even physiomic analyses, and taking advantage of international collaborations, we aim at interrogating unexplored molecular mechanisms underlying several cardiovascular diseases, such as inherited lethal arrhythmia, common arrhythmia, cardiomyopathy, heart failure, and aneurysm.

- Global collaboration of the comprehensive genetic and genomic studies for arrhythmias
- Genetic and proteomic studies of aortic and intracranial aneurysm
- Multi-omics study of dilated cardiomyopathy
- Development of high throughput screening technology to functionally validate ion channel VUSs responsible for lethal arrhythmia (AMED project 2019)
- Epigenetic study of congestive heart failure





Biobank

Precious Human Resources of Cerebral and Cardiovascular Diseases for Research

NCVC Biobank, a non-profit project to collect human biosamples and related health data, greatly appreciates the contributions from more than 17,000 patients (up to July 2019) since our establishment in 2011. We preserve blood, tissues and other biospecimens derived from our patients suffering from cerebral and cardiovascular diseases with detailed medical datasets such as medical history, medication and laboratory data while protecting anonymity. We are also a member of National Center Biobank Network (NCBN) in Japan. [https://ncbiobank.org/organization/index.php]



Dept. Industrial-Academic Collaboration

Promotion of Collaboration to Create Next Generation of Medical Care / Healthcare

Area 201

Collaboration with companies, universities, and medical institutions is essential for the realization and diffusion of innovative medical technologies. By further development of technology seeds based on clinical needs directly linked to the advanced medicine, the Department of Industrial-Academic Collaboration aims to create the next generation of medical devices, pharmaceuticals, and healthcare businesses.

- The solution scheme of clinical needs, and results from studies, are properly protected as intellectual properties
- The results of industry-academic collaboration are appropriately returned to society as new medical care/ healthcare that contribute to the study and cure of cardiovascular diseases



Area 204 Promotion of Education • Training Center

Committed to Improve the Quality of Healthcare through Original Programs

- The Department of Promotion of Education, in conjunction with cardiovascular training center, provides wide range of clinical training systems from elementary medical training equipment to cutting-edge diagnostic and surgical simulators
- Our department is also involved in organizing invited lectures and seminars, managing specific clinical researches, and administration of specific clinical practices of nurses
- The OIC Training Center is the only center in Japan that is exclusive for clinical trainings of cerebral and cardiovascular diseases
- We also concentrate our effort on designing and developing novel medical equipment in collaboration with other OIC members and private companies









Dept. Medical and Health Information Area 206 Management

To Develop Clarification of Cerebral and Cardiovascular Diseases in a Real-Life Setting

Analyzing nationwide dataset in the Center for Cerebral and Cardiovascular Disease Information: The Center is collecting data related to cerebral and cardiovascular diseases throughout Japan to accurately identify the cause of morbidity and other outcomes. For this purpose, the Center administers the Japanese Registry Of All Cardiac and Vascular Diseases (JROAD) Survey jointly with the Japanese Circulation Society, the Japan Stroke databank and Disease Registry and several dense data for cerebral and cardiovascular diseases by electronic data capture (EDC).

The Center's goal is to accurately explore disease-related information, to formulate the detailed dataset by enhancing the in-hospital registration system, to provide the research environment for analyzing the nationwide dataset and give those results back to the people and to investigate common risk factors and solutions for both stroke and cardiovascular diseases by aggregating the nationwide dataset.

