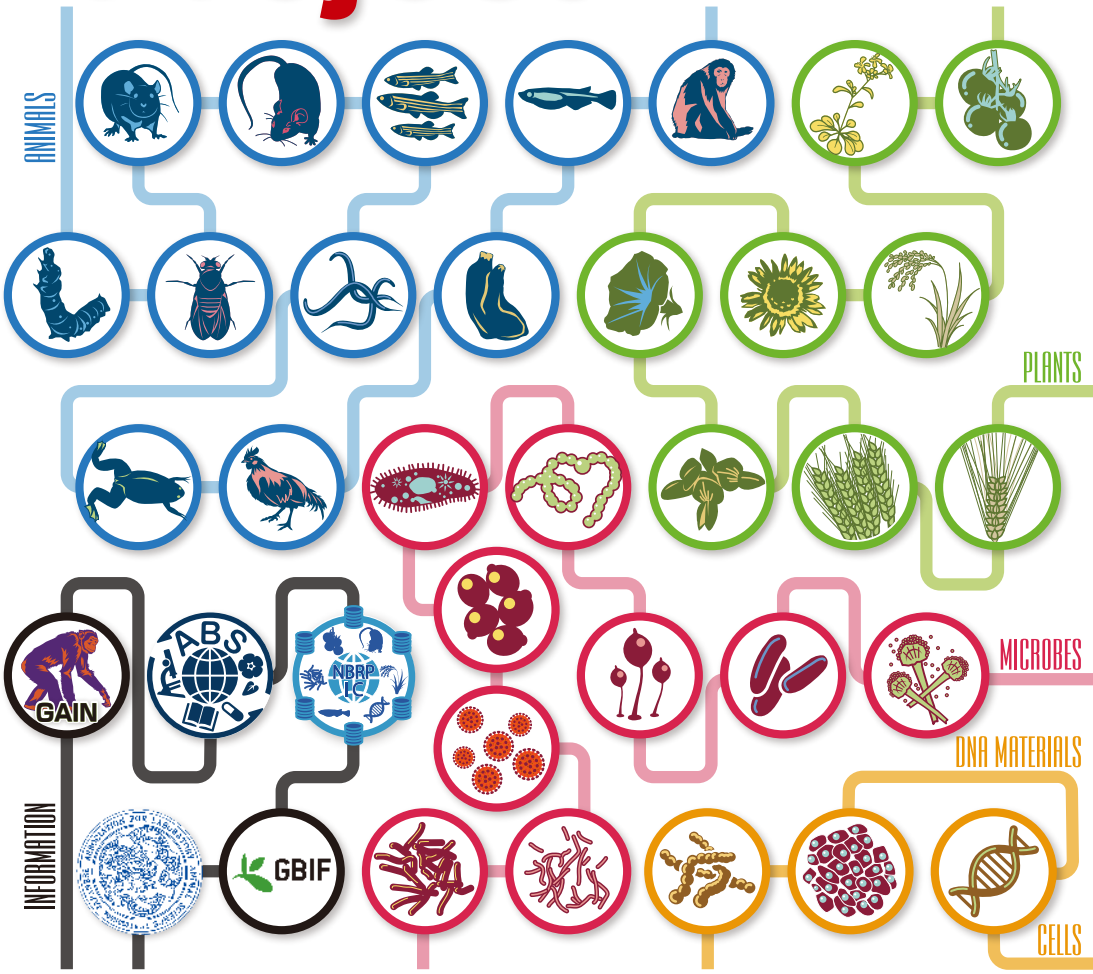
MEXT National BioResource Project

NBRP



Introduction

Bio-resources (strains, populations, tissues, cells, genes of animals, plants and microorganisms, and information on these materials for R&D use) are essential infrastructures for life sciences. It is vital that researchers share the various bio-resources necessary for pursuing research and development. This is because these resources, produced with years of painstaking labor, form the foundations for future research. It is also necessary for scientific communities to use a common set of bio-resources to permit their research results to be effectively compared. The development of outstanding collections of bio-resources is therefore essential to give this country an internationally competitive edge in life sciences.

Based on the Japanese Government's Science and Technology Basic Plans, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) implemented the National BioResource Project (NBRP) in FY2002 to construct a framework for the systematic collection, preservation, and distribution of bio-resources, with a special focus on those that require strategic development by the national government. The NBRP is revised every five years, with the fourth phase having started in FY2017. With the addition of the human pathogenic virus category in FY2020, the current project consists of the cores of 31 categories of bio-resources and the centers for information on these resources. The bio-resource framework has been enhanced by increasing the importance of value-added genomic resources and developing preservation technologies. Several of our bio-resource centers have been acknowledged as meeting the highest global standards.

Based on the Plan for Promotion of Medical Research and Development of the Healthcare Policy approved by the Cabinet in 2014, the Japan Agency for Medical Research and Development (AMED) operated the NBRP from FY2015. In recognition that the NBRP supports the life sciences more broadly, the NBRP is operated again by MEXT from FY2021. Currently, the Program Director (PD) and the Program Officers (PO) are responsible for promoting the activities of the NBRP, taking into consideration the current trends in life sciences.

Finally, I would like to emphasize a lesson we learned from the Great East Japan Earthquake: that the bio-resources in the NBRP cannot be restored once they are lost. Since this disaster struck, we have developed a backup system that includes long-term cryopreservation of bio-resources. Currently, the spread of COVID-19 around the world puts the maintenance and provision of bio-resources at risk due to restricted staff attendance. To solve this problem, we are promoting labor-saving in bio-resources maintenance and the adoption of remote monitoring systems. We will try to preserve the stable maintenance and provision of bio-resources even in the face of crises such as the current one. Your cooperation and support for this project will be highly appreciated.

April 2021

Yuji Kohara, Ph.D.
Program Director, NBRP
(Director, Database Center for Life Science,
Research Organization of Information and Systems,
Inter-University Research Institute Corporation)

National BioResource Project

National BioResource Project

Purpose

The major aim of the National BioResource Project (NBRP) is to collect, preserve, and provide bio-resources (strains, populations, tissues, cells, genes of animals, plants and microorganisms, and information on these materials for R&D use), that are essential experimental materials for life sciences research. To be able to meet current scientific needs, the project also aims to increase the usefulness of these bio-resources via the addition of genome information and development of fundamental technologies for preservation and other necessary procedures. The information center will also be upgraded to promote the dissemination of information on the whereabouts and biological characteristics of these bio-resources.

Background

The Ministry of Education, Culture, Sports, Science and Technology (MEXT) has conducted the National BioResource Project (NBRP) since FY2002 to comprehensively promote life sciences. In the project, the systems of collection, preservation, and distribution were established for bio-resources, such as experimental animals, plants, and microbes (strains, populations, tissues, cells, and genetic materials of animals, plants, and microbes and their information as research and development materials) that require strategic development by the national government.

In the Sixth Science and Technology Basic Plan (FY2021 - FY2026), the government stipulated that intellectual infrastructures and biological and genetic resources such as genetic data that are the foundations of data-driven research should be provided strategically and systematically. The NBRP therefore plans to build on the existing intellectual infrastructure by improving the quality of available resources in response to diverse needs and promote the strategic collection and utilization of these bio-resources.

General Outline

The National BioResource Project is implementing the following four programs to facilitate the collection, preservation, and provision of bio-resources and the development of related technologies: (1) a core facility upgrading program, (2) a genome information upgrading program, (3) a fundamental technology upgrading program, and (4) an information center upgrading program.

These programs will accomplish the purpose of the project described above and will be coordinated to produce synergistic effects.

(1) Core facility upgrading program

The core facilities will be established to carry out the collection, preservation, and provision of bio-resources. The bio-resources selected for the NBRP are of fundamental importance in life sciences research, must be of the highest quality, and must originate in Japan.

(2) Genome information upgrading program

The aim of this program is to improve the quality of bio-resources and increase their value, as well as to reinforce the unique nature and leading position of Japanese bio-resources by enriching and expanding strain and characteristics information, genetic information, such as genome sequences of cDNA, and genome resources, including genome libraries of bio-resources that are collected, preserved, and provided by the NBRP.

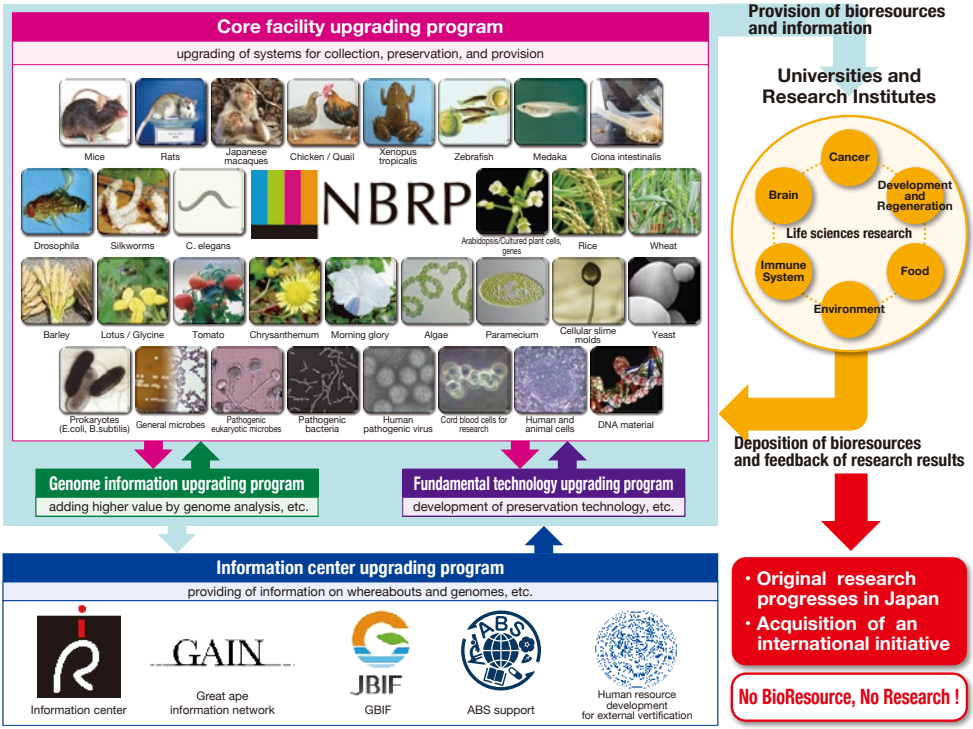
(3) Fundamental technology upgrading program

Development of technologies relating to the collection, proliferation, quality management, preservation and provision of bio-resources that are the subjects of the core facilities promotion program.

(4) Information center upgrading program

Construction and upgrading of databases holding locational information, genetic information and the biological characteristics of bio-resources that are collected at the core facilities, and enhancement of the NBRP's public relations via its website.

Project Aims



How to order and about handling/shipping costs

How to order:

Please go to the “Resource Search” page in the NBRP portal (https://nbrp.jp/en), and click on the resource name you wish to get, which is listed on the website. Then, follow the instructions to proceed.

About handling and shipping costs:

The expenses for handling and shipping will be charged to the recipients.

NBRP portal site

Homepages of individual NBRP Bioresource Databases

List of NBRP Implementing Organizations

Core Facility Upgrading Program

Organism, etc	✳	Principal Investigator	Implementing Organization	Page
Mice	○	Atsushi Yoshiki	Experimental Animal Division, RIKEN BioResource Research Center	1
Rats	○	Masahide Asano	Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University	2
		Tomoji Mashimo	The Institute of Medical Science, The University of Tokyo	
	B	Atsushi Yoshiki	Experimental Animal Division, RIKEN BioResource Research Center	
Japanese macaques	○	Katsuki Nakamura	Primate Research Institute, Kyoto University	3
		Atsushi Nambu	National Institute for Physiological Sciences, National Institutes of Natural Sciences	
Chicken/Quail	○	Kenichi Nishijima	Avian Bioscience Research Center, Nagoya University	4
Xenopus tropicalis	○	Hajime Ogino	Amphibian Research Center, Hiroshima University	5
		Takashi Kato	Faculty of Education and Integrated Arts and Sciences, Waseda University	
		Haruki Ochi	School of Medicine, Yamagata University	
Zebrafish	○	Hitoshi Okamoto	RIKEN Center for Brain Science	6
		Koichi Kawakami	Genetic Resource Center, National Institute of Genetics, Research Organization of Information and Systems	
		Shinichi Higashijima	Exploratory Research Center on Life and Living Systems, National Institutes of Natural Sciences	
	B	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	
Medaka	○	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	7
		Masaru Matsuda	Center for Bioscience Research and Education, Utsunomiya University	
	B	Hitoshi Okamoto	RIKEN Center for Brain Science	
	B	Ryo Akashi	Faculty of Agriculture, University of Miyazaki	
Ciona intestinalis	○	Yasunori Sasakura	Shimoda Marine Research Center, University of Tsukuba	8
		Yutaka Satou	Graduate School of Science, Kyoto University	
		Manabu Yoshida	Misaki Marine Biological Station, Graduate School of Science, The University of Tokyo	
Drosophila	○	Kuniaki Saito	Genetic Resource Center, National Institute of Genetics, Research Organization of Information and Systems	9
		Toshiyuki Takano	KYOTO Stock Center, DGRC, Kyoto Institute of Technology	
		Takeshi Awasaki	Kyorin University, School of Medicine	
Silkworms	○	Yutaka Banno	Institute of Genetic Resources, Faculty of Agriculture, Kyushu University	10
		Toru Shimada	Faculty of Science, Gakushuin University	
		Zenta Kajiura	Faculty of Textile Science and Technology, Shinshu University	
C. elegans	○	Shohei Mitani	Tokyo Women's Medical University School of Medicine	11
Arabidopsis/Cultured plant cells, genes	○	Masatomo Kobayashi	Experimental Plant Division, RIKEN BioResource Research Center	12
Rice	○	Yutaka Sato	Department of Genomics and Evolutionary Biology, National Institute of Genetics, Research Organization of Information and Systems	13
		Toshihiro Kumamaru	Institute of Genetic Resource, Faculty of Agriculture, Kyushu University	
Wheat	○	Ryohei Terauchi	Graduate School of Agriculture, Kyoto University	14
Barley	○	Kazuhiro Sato	Institute of Plant Science and Resources, Okayama University	15
Lotus/Glycine	○	Ryo Akashi	Faculty of Agriculture, University of Miyazaki	16
		Shusei Sato	Graduate School of Life Sciences, Tohoku University	
Tomato	○	Hiroshi Ezura	Tsukuba-Plant Innovation Research Center University of Tsukuba	17
		Koh Aoki	Graduate School of Life and Environmental Sciences, Osaka Prefecture University	
		Kentaro Yano	School of Agriculture, Meiji University	
Chrysanthemum	○	Makoto Kusaba	Laboratory of Plant Chromosome and Gene stock, Graduate School of Integrated Sciences for Life, Hiroshima University	18
Morning glory	○	Eiji Nitasaka	Faculty of Sciences, Kyushu University	19
		Atsushi Hoshino	National Institute for Basic Biology, National Institutes of Natural Sciences	
Algae	○	Masanobu Kawachi	National Institute for Environmental Studies (NIES)	20
		Shinya Uwai	Kobe University Research Center for Inland Seas	
	B	Kazuhiro Kogame	Faculty of Science, Hokkaido University	

Core Facility Upgrading Program

Organism, etc	∗	Principal Investigator	Implementing Organization	Page
Paramecium	○	Masahiro Fujishima	Joint Faculty of Veterinary Medicine, Yamaguchi University	21
Cellular slime molds	○	Yoichiro Kamimura	RIKEN Center for Biosystems Dynamics Research	22
		Hidekazu Kuwayama	Faculty of Life and Environmental Sciences, University of Tsukuba	
Yeast	○	Taro Nakamura	Graduate School of Science, Osaka City University	23
		Minetaka Sugiyama	Faculty of Life Sciences, Hiroshima Institute of Technology	
	B	Kenji Kitamura	Natural Science Center for Basic Research and Development, Hiroshima University	
Prokaryotes (E.coli, B.subtilis)	○	Hironori Niki	Genetic Resource Center, National Institute of Genetics, Research Organization of Information and Systems	24
	B	Tsutomu Katayama	Faculty of Pharmaceutical Sciences, Kyushu University	
General microbes	○	Moriya Ohkuma	Microbe Division/Japan Collection of Microorganisms (JCM), RIKEN BioResource Research Center	25
Pathogenic eukaryotic microbes	○	Takashi Yaguchi	Medical Mycology Research Center, Chiba University	26
		Osamu Kaneko	Institute of Tropical Medicine (NEKKEN), Nagasaki University	
Pathogenic bacteria	○	Kaori Tanaka	Center for Conservation of Microbial Genetic Resource, Gifu University	27
		Tetsuya Iida	Research Institute for Microbial Diseases, Osaka University	
	B	Haruyoshi Tomita	Laboratory of bacterial drug resistance, Gunma University Graduate school of Medicine	
Human pathogenic virus	○	Jiro Yasuda	Institute of Tropical Medicine (NEKKEN), Nagasaki University	28
		Hirofumi Sawa	Research Center for Zoonosis Control, Hokkaido University	
		Yasushi Kawaguchi	Institute of Medical Science, The University of Tokyo	
		Takeshi Kobayashi	Research Institute for Microbial Diseases, Osaka University	
		Yoshihiro Miwa	Gene Engineering Division, RIKEN BioResource Research Center	
Cord blood cells for research	○	Tokiko Nagamura-Inoue	Department of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science, The University of Tokyo	29
		Yukio Nakamura	Cell Engineering Division, RIKEN BioResource Research Center	
Human and animal cells	○	Yukio Nakamura	Cell Engineering Division, RIKEN BioResource Research Center	30
DNA material	○	Yoshihiro Miwa	Gene Engineering Division, RIKEN BioResource Research Center	31

∗ ○ : Core Facility None : Sub-Core Facility B : Sub-Core Facility for the backup of bioresource

Information Center Upgrading Program

Subject	∗	Task	Principal Investigator	Implementing Organization	Page
Information	○	Development of the Bioresource DBs, etc.	Shoko Kawamoto	Genetic Resource Center, National Institute of Genetics, Research Organization of Information and Systems	32
		GAIN	Genichi Idani	Wildlife Research Center, Kyoto University	33
		GBIF	Utsugi Jinbo	Center for Colletions, National Museum of Nature and Science	
			Shigeto Dobata	Graduate School of Arts and Sciences, The University of Tokyo	
		ABS Support	Mutsuaki Suzuki	NIG INNOVATION, National Institute of Genetics, Research Organization of Information and Systems	34
			Katsuya Fukami	Material Management Center, Kyushu University	
			Noriaki Murakami	Makino Herbarium, Tokyo Metropolitan University	
			Kazuo Watanabe	Tsukuba Plant Innovation Research Center, University of Tsukuba	
		Public Relations	Ayumi Koso	Public Relations Office, National Institute of Genetics, Research Organization of Information and Systems	—
Human resource development for external verification	○		Chihiro Koshimoto	Japanese Association for Laboratory Animal Science	35

∗ ○ : Core Facility None : Sub-Core Facility

Genome Information Upgrading Program

Organism, etc	Principal Investigator	Organization	Focus	Project Period
Rice	Yutaka Sato	National Institute of Genetics	Genome Sequencing of *Oryza* species II	FY2020
Mice	Toyoyuki Takada	RIKEN BioResource Research Center	Long-read sequencing of disease model mouse strains established in Japan	
Morning glory	Atsushi Hoshino	National Institute for Basic Biology	Collecting and providing information on genetic variations of 100 Japanese morning glory lines	
Rice	Yutaka Sato	Department of Genomics and Evolutionary Biology, National Institute of Genetics	Genome sequencing of *Oryza* species	FY2019
Wheat	Shuhei Nasuda	Graduate School of Agriculture, Kyoto University	Genome Sequencing of parental accessions of the NAM population of East Asian wheat	
X. tropicalis	Hajime Ogino	Amphibian Research Center, Hiroshima University	Generation of the genome polymorphism data of *Xenopus tropicalis* inbred strains	FY2018
Zebrafish	Koichi Kawakami	Department of Developmental Genetics, National Institute of Genetics	Genetic analysis of zebrafish transgenic and inbred lines	
Drosophila	Kuniaki Saito	Genetic Resource Center, National Institute of Genetics	Sequencing genome-editing strains of Drosophila	
Silkworms	Toru Shimada	Graduate School of Agricultural and Life Sciences, The University of Tokyo	Genome re-sequencing of large body-sized strains of the silkworms suitable for pharmacological, physiological and pathological studies	
Chrysanthemum	Makoto Kusaba	Laboratory of Plant Chromosome and Gene stock, Graduate School of Science, Hiroshima University	Whole genome sequencing of the model strain for the genus Chrysanthemum using long read sequencing technology	
Mice	Toyoyuki Takada	Genetic Strains Research Center, National Institute of Genetics	Genome resequencing of Japanese fancy mouse-derived JF1/Ms strain	FY2017
Wheat	Shuhei Nasuda	Graduate School of Agriculture, Kyoto University	Garnering fundamental information on wheat genomic diversity through *de novo* sequencing of the standard Japanese wheat cultivar Norin 61.	
Mice	Toyoyuki Takada	Genetic Strains Research Center, National Institute of Genetics	Genome resequencing of Japanese wild mouse-derived MSM/Ms strain	FY2016
Rats	Mikita Suyama	Medical Institute of Bioregulation, Kyushu University	Whole genome resequencing of the representative rat strains and development of a SNP typing kit	
Silkworms	Toru Shimada	Graduate School of Agricultural and Life Science, The University of Tokyo	Genome Re-sequencing of Diverse Strains of *Bombyx mori* and *B. mandarina* (2)	
Algae	Yuu Hirose	Toyohashi University of Technology	Genome sequencing project of heterocystous cyanobacteria in the NIES collection	
Mice	Yoichi Gondo	RIKEN BioResource Center	Sequence and structure determination and open to public of reference mouse genome based on long one-molecule sequencing.	FY2015
Rats	Mikita Suyama	Medical Institute of Bioregulation, Kyushu University	Targeted genome resequencing of 20 strains of the rats	
Drosophila	Shu Kondo	Genetic Resource Center, National Institute of Genetics	Genome sequencing of diverse *Drosophila* species (II)	
Silkworms	Toru Shimada	Graduate School of Agricultural and Life Science, The University of Tokyo	Genome Re-sequencing of Diverse Strains of *Bombyx mori* and *B. mandarina*	
Lotus	Shusei Sato	Graduate School of Life Sciences, Tohoku University	Generation of high quality genome sequence of Gifu accession of *Lotus japonicus* to accelerate NBRP resource application	
Pathogenic microorganisms	Takashi Yaguchi	Medical Mycology Research Center, Chiba University	Maintenance of whole genome sequences on related species of *Aspergillus fumigatus*	
Rice	Nori Kurata	Genetic Resource Center, National Institute of Genetics	Generation of genome sequence diversity information for wild relatives of rice	FY2014
General microbes	Moriya Ohkuma	Microbe Division/Japan Collection of Microorganisms (JCM), RIKEN BioResource Center	Genome sequencing of eukaryotic microorganisms of NBRP general microbes	
Lotus	Shusei Sato	Graduate School of Life Sciences, Tohoku University	Resequencing of the NBRP collected resources intended to upgrade the genome information of *Lotus japonicus*	
Drosophila	Shu Kondo	Genetic Resource Center, National Institute of Genetics,	Genome sequencing of diverse Drosophila species	

Genome Information Upgrading Program

Organism, etc	Principal Investigator	Organization	Focus	Project Period
General microbes	Moriya Ohkuma	Microbe Division/Japan Collection of Microorganisms (JCM), RIKEN BioResource Center	Genome sequencing of microbial strains for environmental and health science	FY2012
Pathogenic microorganisms	Takayuki Ezaki	GTC Genetic Resource Stock Center of Microbial Pathogens Graduate School of Medicine, Gifu University	Genome Sequencing of Opportunistic Pathogens	
Rat	Tadao Serikawa	Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University	Whole genome sequencing of F344 rat	FY2011
Ciona intestinalis/ Oxycomanthus japonicus	Kazuo Inaba	Shimoda Marine Research Center, University of Tsukuba	Genome sequencing of the *Ciona intestinalis* inbred line	
Mice	Atsushi Yoshiki	Experimental Animal Division, RIKEN BioResource Center	Completion of BAC end sequencing of the mouse C57BL/6N substrain	FY2010
Tomato	Koh Aoki	Kazusa DNA Research Institute	Micro-Tom genome sequencing	
Japanese macaques	Tadashi Isa	National Institute for Physiological Sciences, National Institutes of Natural Sciences	Japanese macaque genome sequencing	
Medaka	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	Establishment of polymorphism information of medaka inbred strains	
Mice	Atsushi Yoshiki	Experimental Animal Division, RIKEN BioResource Center	BAC end sequencing of the mouse C57BL/6N substrain	FY2009
Medaka	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	Full-length cDNA resources of medaka fish	
Wheat	Yasunari Ogihara	Kihara Institute for Biological Research, Yokohama City University	Full-length cDNA resources of common wheat	
Tomato	Erika Asamizu	Gene Research Center, Graduate School of Life and Environmental Sciences, University Tsukuba	Micro-Tom BAC end sequencing	
Medaka	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	Medaka Fish Full-length cDNA Resources	FY2008
Rats	Tadao Serikawa	Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University	Rat LE/Stm BAC end sequencing	
Tomato	Koh Aoki	Kazusa DNA Research Institute	Enhancing tomato resources by sequencing Micro-Tom full-length cDNA	
Medaka	Kiyoshi Naruse	National Institute for Basic Biology, National Institutes of Natural Sciences	Full-length cDNA resources of medaka fish	FY2007
Drosophila	Ryu Ueda	Genetic Strains Research Center, National Institute of Genetics	Genome and property information for the quality control of *Drosophila* strains	
Arabidopsis	Masatomo Kobayashi	Experimental Plant Division, RIKEN BioResource Center	Sequence analysis of full-length cDNAs of *Thellungiella halophila* as new *Arabidopsis* resources	
Wheat	Yasunari Ogihara	Kihara Institute for Biological Research, Yokohama City University	Full-length cDNA resources of bread wheat	

Fundamental Technology Upgrading Program

Organism, etc	Principal Investigator	Organization	Focus	Project Period
General microbes, Pathogenic eukaryotic microbes, Pathogenic bacteria	Rikiya Endo	RIKEN BioResource Center	Development of reference MALDI-TOF MS data that enables rapid identification of various microbes	FY2020-2021
Drosophila	Takano Toshiyuki	Kyoto Institute of Technology	Upgrading and verification of cryopreservation methods of Drosophila stocks	
Mice	Yumiko Saga	National Institute of Genetics	Development of degron-mediated protein knockout applicable to mouse system	FY2019-2020
Rats	Masahide Asano	Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University	Development of reproductive engineering in rats; the effective operation and the expansion of new users	
Zebrafish	Koichi Kawakami	Department of Gene Function and Phenomics, National Institute of Genetics	Development of transgenic fish lines that label and manipulate specific cell types	
Mice	Fumio Ike	Experimental Animal Division, RIKEN BioResource Research Center	Genome Sequencing of Mouse Monitoring Organisms	FY2018-2019
Japanese macaques	Katsuki Nakamura	Primate Research Institute, Kyoto University	Development of a highly sensitive detection system for Japanese monkey B virus DNA	
Chicken/Quail	Yoichi Matsuda	Avian Bioscience Research Center, Nagoya University	Development of cryopreservation methods of chicken PGCs	
Chicken/Quail	Yoshiaki Nakamura	Graduate School of Biosphere Science, Hiroshima University	Sophistication of the cryopreservation of avian germ cells.	
Silkworms	Yutaka Banno	Institute of Genetic Resources, Faculty of Agriculture, Kyushu University	Development of new cryopreservation methods for silkworm and wild silkworm	
Drosophila	Shu Kondo	Genetic Resource Center, National Institute of Genetics	Development of new technologies for stable maintenance of *Drosophila* stocks	FY2017-2018
Rice	Yutaka Sato	Genetic Strains Research Center, National Institute of Genetics	Establishment of experimental basis of genetic transformation for wild accessions of *Oryza* species	
Paramecium	Masahiro Fujishima	Graduate School of Science and Technology for Innovation, Yamaguchi University	Development of reliable cryopreservation method for *Paramecium* genus	
Drosophila	Toshiyuki Takano	Drosophila Genetic Resource Center, Kyoto Institute of Technology	Development of a new cryopreservation method for Drosophila stocks	FY2016
C. elegans	Shohei Mitani	Tokyo Women's Medical University School of Medicine	Construction of High-Performance balancers for *C. elegans*	
Rats/Zebrafish/ X. tropicalis	Takashi Yamamoto	Graduate School of Science, Hiroshima University	Development of easy protocols for efficient gene knock-in using genome editing technology	
Mice	Atsushi Yoshiki	Experimental Animal Division, RIKEN BioResource Center	Fundamental technology development of genome editing for the establishment of intractable disease models	
Silkworms	Yutaka Banno	Institute of Genetic Resources, Faculty of Agriculture, Kyusyu University	Development of cryopreservation methods of the silkworm	FY2014
Mice	Fumihiro Sugiyama	Laboratory Animal Resource Center, University of Tsukuba	Development of Cre-loxP recombination atlas for Cre-driver mouse strains	
Mice	Naomi Nakagata	Center for Animal Resources & Development (CARD), Kumamoto University	Establishment of *in vitro* fertilization systems for all mouse strains	FY2012-2013
Medaka	Goro Yoshizaki	Graduate School of Marine Science and Technology, Tokyo University of Marine Science and Technology	Production of functional gametes derived from cryopreserved germ-line stem cells using a surrogate broodstock system in medaka	
Drosophila	Ryu Ueda	Genetic Resource Center, National Institute of Genetics	Development of cryopreservation method of Drosophila strains	
Rats	Tadao Serikawa	Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University	Improving the efficiency of sperm preservation technologies in rats	FY2010-2011
Mice	Yasumasa Ishida	Graduate School of Biological Sciences, Nara Institute of Science and Technology	Production of conditionally gene-disrupted ES-cell clones and establishment of a database for the inactivated genes	

• Subjects completed by FY2009 are shown on the "Achievements" page in the NBRP portal (https://nbrp.jp/achievements/).

CORE FACILITY UPGRADING PROGRAM Mice

Core Facility : Experimental Animal Division, RIKEN BioResource Research Center
Principal Investigator : Atsushi Yoshiki FAX : +81-29-836-9010
Contact site : animal@brc.riken.jp
URL : https://mus.brc.riken.jp/en/

Overview

Mice are used as model animals for human widely in the life science research and development. To meet social and research needs, the Experimental Animal Division of the RIKEN BioResource Research Center (BRC) has operated to collect, preserve, quality-control and distribute mouse models created in Japan for the study of higher biological functions and conquering diseases. Our mice are cleaned-up to specific pathogen-free state, strictly monitored for their health and genetic modifications. Genomic, gene expression and phenotypic information are added to enrich their value to establish mouse resources of the world highest standard. As an international hub, RIKEN BRC participates in the International Mouse Strain Resource, IMSR and registers strains created by Japanese scientists and disseminate the mice around the world. We have also promoted Asian/Australian networks to strengthen regional cooperation and participated with other BRC groups in the International Mouse Phenotyping Consortium (IMPC) to contribute to basic medical sciences and drug discovery by producing knockout mice for every coding gene, generating broad-based phenotypic data, and making them available to scientists around the world (*Nat Genet* 53(4): 416-419, 2021).

International collaboration

International Mouse Strain Resource, IMSR One-Stop Shop Database
http://www.findmice.org/

Asian Mouse Mutagenesis & Resource Association, AMMRA
http://www.findmice.org/

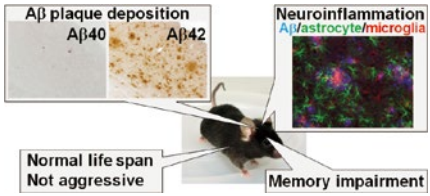
International Mouse Phenotyping Consortium, IMPC
http://www.mousephenotype.org/

Key Strains/Studies

We have approximately 9,000 mouse strains as follows: inbred mice, spontaneous and induced mutants, Cre and FLP driver strains and transgenic mice to visualize various phenomena, mice with targeted mutations such as knock-out and knock-in, congenic strains, strains with chromosomal abnormalities and chromosomal recombination, and wild-derived mouse strains.

● C57BL/6-*App*$^{tm3(NL\text{-}G\text{-}F)Tcs}$/*TcsRbrc* (RBRC06344)

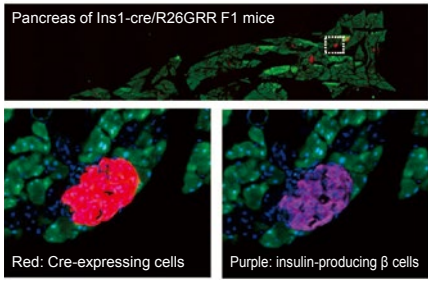
Drs. Saido, Saito, and colleagues at RIKEN Brain Science Institute have developed the next generation mouse models for Alzheimer's disease (AD) by knock-in to the *App* gene with *Swedish* (NL), *Iberian* (F) and *Arctic* (G) mutations found in familial AD patients. This mouse model well recapitulates patients' amyloid pathology (Fig.1) and is expected to become a standard model to find preventive therapies of the AD (*Nat Neurosci* 17, 661-3, 2014).



Courtesy of Drs. Takaomi C. Saido and Takashi Saito
Fig. 1. Alzheimer's disease model with human patients' mutations

● C57BL/6-*Gt(ROSA)26*$^{tm1(CAG\text{-}EGFP/DsRed)Utr}$ (R26GRR)

Dr. Sugiyama, University of Tsukuba in the FY2014 NBRP Fundamental Technologies Upgrading Program characterized Cre-driver strains such as genome-edited knockin B6-*Ins1*$^{em1(cre)Utr}$ mice (RBRC09525) and improved the technology to evaluate the tissue specificity of Cre-recombinase expression by using R26GRR mice (RBRC0487) (Fig.2, *Exp Anim* 65, 319-27, 2016).



Courtesy of Dr. Fumihiro Sugiyama
Fig. 2. Pancreatic β cell -specific Cre recombinase expression in the Ins1-cre mice

CORE FACILITY UPGRADING PROGRAM Rats

Core Facility : Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University
Principal Investigator : Masahide Asano FAX : +81-75-753-4409
Contact site : nbrp-adm@anim.med.kyoto-u.ac.jp
URL : http://www.anim.med.kyoto-u.ac.jp/NBR

Overview

The rat is the mammal which is used in many fields of research owing to its suitable size, adaptability and neurological characteristics. Recent developments including the establishment of rat ES/iPS cells and the generation of gene knockout rats using gene editing nucleases (ZFN/TALEN/Cas9) technology etc. will boost the utility of the rat as biological resource.

Various rat strains deposited to NBRP-Rat

The Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, conducts a rat strain-based collection, preservation and distribution program and quality assurance through microbial and genetic monitoring, enhances rat strain databases and holds the Rat Resource Research Meeting to support and stimulate science in the rat research community. Riken BRC, backs up frozen embryos and sperm, and the University of Tokyo, preserves and supplies immunodeficient rats, respectively, to support the central facility at Kyoto University as a sub center.

The NBRP-Rat has been developed with the intent of being the world's leading rat resource center. This project promotes further utilization of the rat as a research tool in many fields of science.

Key Studies

So far, approximately 900 different strains have been deposited to NBRP-Rat. The repository includes spontaneous mutants, recombinant inbred, congenic, consomic, transgenic, and knock out rats. These strains are utilized in fields as neurobiology, cardiovascular disease/hypertension, diabetes/obesity, cancer, immunology, development and metabolism.

● Severe combined immunodeficiency rats (X-SCID, SCID, FSG)

Immunodeficient rats were established using gene editing nucleases (ZFN/TALEN). These strains can act as hosts for human xenogeneic tissue grafts and stem cell transplantation.

● Reporter gene transgenic rats

GFP, DsRed, LacZ and other marker genes are important tools for the examination of many biological processes. Our repository has many of such marker strains available for various kinds of experiments with ubiquitous or organ specific marker expression.

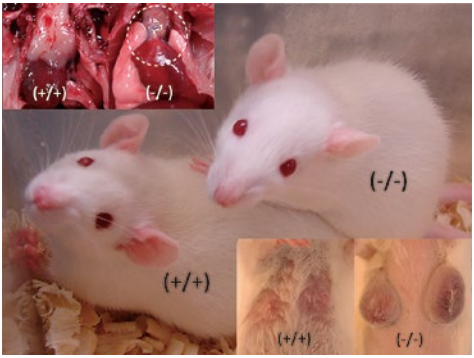


Fig.1 X-SCID Rat (+/+ : Wild type, -/- : *Il2rg* mutated). Left upper : Lack of thymus, Right lower : Xenoplantation of human tumor cells.

● KURMA (Kyoto University Rat Mutant Archive)

Sperm and DNA of 10,752 ENU mutagenized F344 G1 animals are integrated into the NBRP-Rat. This mutant archive, KURMA10K, provides gene-targeted rats as animal models for various fields in biomedical research.

Japanese macaques

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Overview

The Japanese macaque is a middle-sized monkey similar to the rhesus macaque and the long-tailed macaque. These are all classified into the genus *Macaca* and belong to the *Cercopithcinae*. Monkeys of the genus *Macaca*, so-called macaques, are relatively close to humans and are indispensable experimental animals for research on higher brain functions, infections/immunology, and regenerative medicine.

A Japanese macaques parent and child at the Primate Research Institute of Kyoto University

The Japanese macaques, which are indigenous to Japan, have often been used in the fields of neuroscience and physiology in Japan. They have a very high level of curiosity and are temperate in nature. In addition, Japanese macaques are genetically less variable and exhibit more complex cognitive functions than other macaque monkeys that commonly inhabit Southeast Asia. Because the amount of ecological, behavioral, genetic and morphological literature available concerning Japanese macaques is the largest for all monkey species, it is regarded as an extremely useful experimental animal.

In the 4th phase of NBRP, the core facility, Kyoto University Primate Research Institute, keeps promoting the project, jointly with the sub-core facility, National Institute for Physiological Sciences. When providing Japanese macaques, we conduct the following basic tests: body weight and appearance, tuberculin reaction, Shigella, salmonella, simian varicella virus antibody, B virus, and simian retrovirus. In addition, monkeys are sorted in advance according to the research purpose such as sex, age, and physical characteristics to meet the needs of researchers.

Key Studies

The followings are findings obtained by studies using Japanese macaques: the discovery of the prefrontal brain areas essential for meta mnemonic decision-making via fMRI (*Science* 355: 188-193, 2017), and elucidation of brain mechanisms by which self- and other-reward information is integrated into a subjective value (*Nat Neurosci* 21: 1452-1462, 2018), presentation of the evidence that Japanese macaques show theory of mind-based behaviors, and identification of the brain area involved in this capacity (*Cell Reports* 30(13): 4433-4444.e5, 2020), success in evoking forelimb movements using optogenetic stimulation of the macaque motor cortex (*Nat Commun* 11: 3253, 2020), development of a new high-affinity and selective agonist, deschloroclozapine (DCZ), which specifically acts on a designer receptor that serves as a "switch" in the brain (Fig 1. *Nat Neurosci* 23: 1157-1167, 2020). As such, many studies using Japanese macaques have been published in Japan.

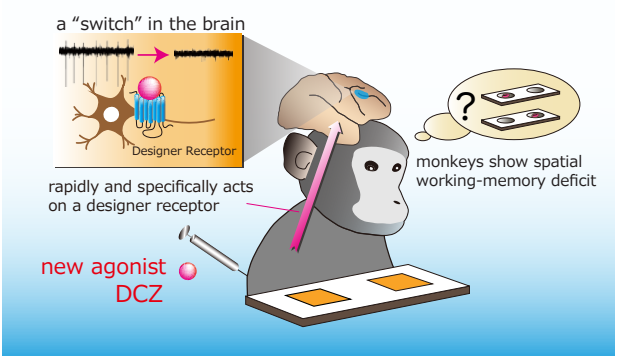

Fig 1. The new agonist, deschloroclozapine (DCZ), selectively and rapidly induces spatial working-memory deficit in monkeys expressing designer receptors in the prefrontal cortex. DCZ was effective shortly after administration at an about 1/100 dose of previous agonists, and the effect disappeared after 24h. DCZ should facilitate the understanding of the pathology of psychiatric and neurological diseases and lead to the development of safe and on-demand therapeutic methods.
 (*Nat Neurosci* 23: 1157-1167, 2020)

CORE FACILITY UPGRADING PROGRAM Chicken / Quail

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Overview

The chicken and quail are important model organisms in life sciences, which bridge the evolutionary gap between mammals and other vertebrates and serve as the main laboratory models for ~9,600 extant avian species. Avian Bioscience Research Center (ABRC), Nagoya University contributes to advancement of avian science research as the core facility of avian resources under NBRP.

The ABRC develops the stable system to maintain, preserve and distribute chicken and quail resources with promoting collection of bird resources available throughout Japan. We are offering high-quality resources by developing and upgrading strains under strict genetic control. Furthermore, we are working to collect new genetically modified chickens using recently developed CRISPR-Cas9 technology and develop the cryopreservation technology for germ cells. In addition, we construct the database of the resources, which is widely open to the public via the homepage, and enhance it by adding science-based information obtained using the resources. We have also generated a high quality chromosome-scale assembly of the Japanese quail genome in collaboration with the Quail Genome Consortium of Japan and published it from our homepage (http://viewer.shigen.info/uzura/index.php).

Website releasing assembly information of the Japanese quail genome

Key Strains/Studies

The ABRC distributes 38 strains and/or lines of chickens including the red junglefowl (the wild ancestor of domesticated chickens), inbred strains, and models for human diseases, and 24 lines of Japanese quail including standard lines and a variety of plumage color mutants. Moreover, we distribute transgenic chicken and quail lines that express fluorescent proteins.

● GSP

A highly inbred strain originated from the Fayoumi chicken breed native to Egypt. Skin grafts are acceptable between different individuals. The genotyping of microsatellite DNA markers revealed that 54 loci used for genetic monitoring are fixed in less than 1% heterozygous condition, indicating that this strain is very suitable for experiments for which high reproducibility and accuracy are required.

GSP

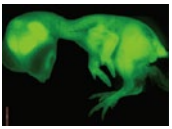
● WE

A Japanese quail line that lays white-shelled eggs, which has been maintained as a closed colony for more than 50 years. This line is used as a standard line for producing vaccine of Marek's disease and toxicity assays of chemicals including pesticides.

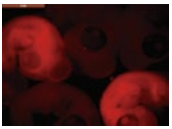
WE

● pLSi/ΔAeGFP-TG chicken and PGK:H2B-chFP-TG quail

Transgenic chicken and quail lines carrying fluorescent protein genes. The chicken and quail lines express enhanced green fluorescent protein (eGFP) and monomer cherry fluorescent protein (chFP), respectively, in the almost whole body.



pLSi/ΔAeGFP-TG



PGK:H2B-chFP-TG

CORE FACILITY UPGRADING PROGRAM Xenopus tropicalis

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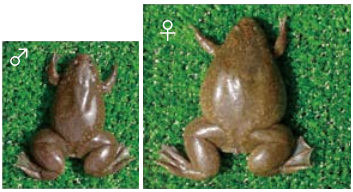
Overview

Xenopus tropicalis is a closely related species of *Xenopus laevis* that has been used widely as a model animal for developmental biology. The experimental system of *X. tropicalis* has been developed recently, by virtue of its characteristics suitable for genetic studies, such as a compact diploid genome (nearly half size of the human genome) and a short life cycle (4–6 months). The genome project has revealed that more than 79% of the genes involved in human diseases are present as orthologues in *X. tropicalis* (*Science* 328: 633-636, 2010). The gene functions can be easily examined by CRISPR-Cas9 system, which disrupts 80~99% of the target genes in founder embryos (*Genes Cells* 21: 755-771, 2016). Transgenesis also works quite efficiently with I-SceI meganuclese method, in which introduced transgenes are transmitted to offspring from the founder animals (*Nat Protoc* 1: 1703-1710, 2006).

In this project, the Hiroshima University Amphibian Research Center collects, preserves and provides living and non-living resources of *X. tropicalis* as the core facility. Waseda University, Nihon University and Yamagata University are in charge of strain preservation as the backup partner facilities. Under this arrangement, we are working together to improve the infrastructure of this new model animal, and to support the resource users for further development of amphibian genetics. As part of such activities, we are generating inbred lines, and hold technical training sessions on breeding methods, transgenesis and genome editing, and bioinformatics analysis every year.



Xenopus tropicalis (Nigerian H strain)

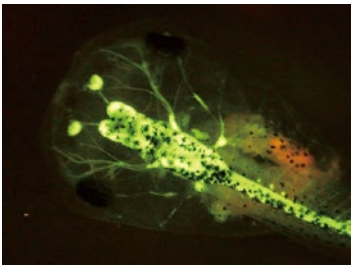


Fig. 1. A transgenic tadpole expressing GFP in the central nervous system under the control of a cis-regulatory region of *Xenopus tropicalis β-tubulin* gene.

Key Strains/Studies

Currently our main resources are four inbred wild-type strains, Nigerian A (a derivative from the "original" Nigerian strain used for the first genome-sequencing project), Nigerian H (genetically close to Nigerian A but easier on breeding), Nigerian-BH (previously referred as "Golden", genetically close to Nigerian A but very robust), and Ivory Coast (a robust strain genetically diverged from the Nigerian group). The whole genome sequences of these four strains are available in public (https://xenopus.nbrp.jp/NBRP_Xenopus/genome_browser.html). We are also collecting transgenic lines useful for live-imaging of stem/differentiated cells (Fig. 1, *Tg(tnbb2b:GFP)1Ogino*). We are supplying 3,000 frogs and tadpoles to researchers and educators every year. Genomic DNA, RNA, and marker gene plasmids are also available as part of the resources.

X. tropicalis is used in various research fields, such as elucidation of the mechanisms of how fins evolved to fingers (Fig. 2, *Dev Cell* 50: 155-166, 2019), discovery of nephric tubule regeneration factor (*eLife* 8: e43186, 2018), and elucidation of the mechanisms underlying the pathogenesis of Hermansky-Pudlak syndrome, a human hereditary disease (*Dev Biol* 426: 472-486, 2017).

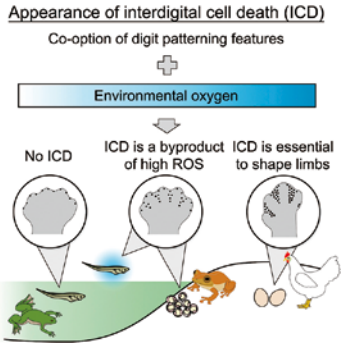


Fig. 2. Exposure of developing embryos to oxygen is essential for reactive oxygen species (ROS)-mediated Interdigital cell death (From *Dev. Cell* 50: 155-166, 2019).

CORE FACILITY UPGRADING PROGRAM Zebrafish

Core Facility : RIKEN Center for Brain Science
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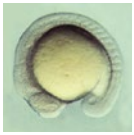
Overview

Zebrafish is classified as a vertebrate, and their embryos are transparent. Additionally, breeding is easy, life cycle is short, and introduction of mutation and genetic modification is easy. Therefore, they are used for studies on biological regulatory processes such as development and regeneration using molecular genetics and imaging technology. In recent years, reflecting the spirit of animal welfare, the demand as a substitute for mammalian models has also increased.

adult

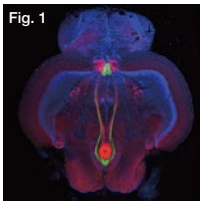


Embryo: 16 hours after fertilization

The number of zebrafish researchers in Japan is increasing. Accordingly, the number of mutant lines and transgenic lines generated in Japan is also rapidly increasing. An efficient sperm freezing technology has been developed on the "fundamental technology upgrading program" in the NBRP. Under these circumstances, the major aim of this project is to set up a system for collecting, maintaining and distributing fish lines for the following purposes: (1) to supply researchers in Japan with lines of their interests quickly. (2) to supply researchers in foreign countries with zebrafish lines created in Japan to increase Japan's contribution to the community. The RIKEN Center for Brain Science (CBS) as the core facility, and the Genetic Resource Center at National Institute of Genetics and the Exploratory Research Center on Life and Living Systems at National Institutes of Natural Sciences as partner organizations jointly maintain the system to collect, preserve, and distribute zebrafish.

Key Strains/Studies

The roles of the three institutes are as follows. RIKEN CBS: Strains with spontaneous and chemically or genetically induced mutant strains, transgenic strains, and wild-type strains. National Institute of Genetics: Transposon insertion, enhancer trap, and exon trap strains. National Institutes of Natural Sciences: Transgenic lines. Cumulatively, the number reaches approximately 6,000 lines.

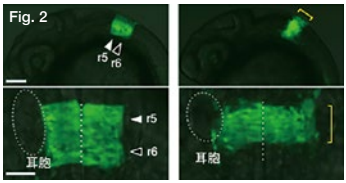


● dao:cre-mCherry; vglut2a:loxP-DsRed-loxP-GFP (RIKEN CBS)

Habebulo-raphe pathway (shown in green), a conserved neural circuit among the vertebrates, encodes the expected level of aversiveness for learning appropriate behavior to avoid the danger (Fig. 1, *Neuron* 87: 1034 1048, 2014).

● gSAIzGFFM35A; UAS:GFP (National Institute of Genetics)

We have created more than 1,000 gene trap and enhancer trap transgenic zebrafish lines that express yeast transcription factor Gal4 in specific tissues, cells, and organs. By crossing these Gal4 lines with transgenic fish lines in which a fluorescent reporter gene or an effector gene that inhibits or manipulates cell functions is placed downstream of upstream activator sequence (UAS), which is a recognition sequence for Gal4, the reporter or effector can be expressed in a tissue-, cell-, or organ-specific manner. The gSAIzGFFM35A line carries a gene-trap transposon insertion in the transcription factor mafba gene. GFP is specifically expressed in the rhombencephalon (r5, r6), and dysplasia of this region is observed in homozygous diploid embryos (Fig. 2, *Cell Rep* 24: 1562-1572, 2018).

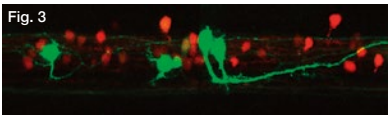


gSAIzGFFM35A; UAS:GFP Heterodiploid

gSAIzGFFM35A; UAS:GFP Homodiploid

● chx10: loxP-DsRed-loxP-GFP (National Institutes of Natural Sciences)

This strain uses the Cre–loxP system. Normally, DsRed is expressed in all alx-positive cells, but by using Cre, it is possible to express EGFP instead of DsRed in some (or all) alx-positive cells (Fig. 3, *J Neurosci* 26: 5684-5697, 2006).



CORE FACILITY UPGRADING PROGRAM Medaka

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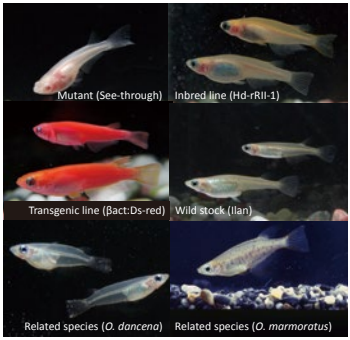
Facebook : https://www.facebook.com/nbrpmedaka/

Overview

Medaka, which can survive in a wide temperature range (4°C–37°C), has been used for more than 100 years as an experimental animal, and many bioresources have been accumulated by the enormous efforts of the predecessors. Furthermore, related species inhabit various environments such as freshwater or seawater. Using genetically distinct inbred strains and various strains such as wild-derived strains and related species from various regions throughout Southeast to Eastern Asia, we can study evolution in an order of millions to 10 millions of years. Genomic resources such as BAC, Fosmid, or cDNA clones are well maintained along with live resources such as inbred strains, wild stocks, related species, transgenic lines, mutants, etc. The whole genome sequence of three inbred strains is available.



Various medaka strains offered by NBRP-Medaka.

In the 4th phase of NBRP, collection, preservation, and provision of medaka resources are carried out by National Institutes for Basic Biology (NIBB) and Utsunomiya University and the backup preservation of the clone and the frozen sperm is handled by Miyazaki University and the RIKEN. These four institutions/universities will cooperate to provide the world's best medaka resources covering a wide range from primary education to cutting-edge medical and biological research. In addition, NIBB created an environment where any medaka community members can use reverse genetics techniques by providing a TILLING library and a CRISPR–Cas9 genome editing platform.

Key Strains/Studies

We preserve and provide more than 6,000 lines, including d-rR strain (males and females can be discriminated with body color), Quintet, STII, STIII lines (transparent body due to lack of most pigment cells), inbred strains (Hd-rR, HNI, Kaga, HSOK, etc.), wild stocks (wild medaka collected from Japan, China and Korea), transgenic lines (osx:mCherry/col10a1:nlGFP osteoblast/ osteoclast visualizing line, GaudiLxBBW and GaudiBBW 2.1 brainbow cassette expression line, FmpoP :RFP-Lifeact bone marrow-derived cell visualization line), closely related medaka species (Celebes medaka, Indian medaka, Javanese medaka etc.), and TILLING lines.

They are used in the following broad areas of research: identification of the second vertebrate sex-determining gene, *Dmy* and novel sex-determining genes $Gsdf^{Y}$ and $Sox3^{Y}$ (Fig. 1: *Nature* 417: 559-563, 2002, etc), identification of causal genes of mutants (body color mutants, cystic kidney disease, double anal fins, *glucocerebrosidase* (*GBA*) gene mutation *etc*.) to develop human disease models such as melanoma, Parkinson disease, etc. (Fig. 2: *PLoS Genet* 11: e1005065, 2015), discovery of a switch gene *Foxl3* determining the sex of germ cells (*Science* 328: 1561-1563, 2010; *Science* 349: 328-331, 2015), elucidation of the molecular neural basis for mate choice and social interactions (*Science* 343: 91-94, 2014), the first discovery of "face inversion effect" in non-mammalian vertebrates (Fig. 3, *elife* 6: e24728, 2017), and toxicity test using medaka embryos and adults. About 20% of the total shipments of fish is to overseas (USA, Germany, Spain, Canada, Korea, China etc.).

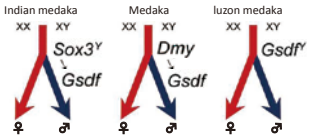


Fig. 1. Diversification of sex-determining genes in the genus *Oryzias*.

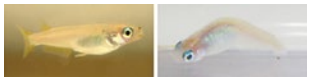


Fig. 2. Decreased function of *GBA* is a risk factor for the onset of Parkinson's disease. Unlike *GBA* deficient mice, *GBA* deficient medaka is not lethal and shows a bent posture (From *PLoS Genet* 11: e1005065, 2015, Fig. 1C).

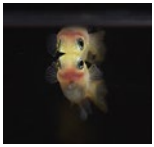


Fig. 3. The face turned upside down is reflected on the water surface. (From the University of Tokyo · Okayama University press release 'Medaka distinguishes friends by "face"' Photographed by Mr. Eiji Fujiwara in the documentary channel).

Ciona intestinalis

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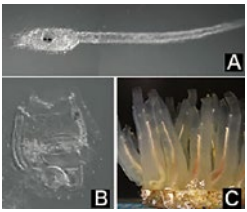
Overview

Marine invertebrates are excellent materials for various subjects of researches including embryogenesis, evolution, reproduction and neurophysiology. In marine invertebrates, ascidians are the closest living relatives of vertebrates, and share the chordate-specific characteristics including the dorsal neural tube, notochord, pharyngeal gill and endostyle/thyroid gland with vertebrates.

Ciona intestinalis is the model species of ascidians because of well-annotated genome sequence and accumulated EST/cDNA/protein resources. The genomic analyses have shown that this ascidian has the basic set of the genes for constructing chordate body plan with less redundancy of gene functions. *Ciona intestinalis* is an excellent organism to perform genetic analyses for understanding gene functions owning to its simple genome and body organization. The inland culture system, transposon-based transgenesis, mutagenesis and knockouts by genome editing have been developed in *Ciona*. By using these genetic technologies, various transgenic and mutant lines have been created which are splendid tools for studying gene functions. The mission of this Bioresource project is collecting, maintaining and supplying wild types, transgenic/mutant lines and plasmid DNAs used in *Ciona* studies.



(A) Juveniles of *Ciona intestinalis*: During the juvenile period, they actively swim in the form of tadpoles. (B) *C. intestinalis* immediately after metamorphosis: After metamorphosis, it loses its tail and enters sedentary life. (C) Adults of *C. intestinalis*.

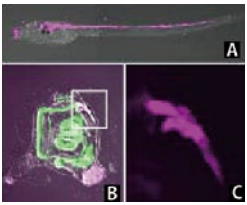


Fig. 1. Trace experiment in metamorphosis process of cells of larval nervous system using Kaede. (A) Larva: Neuronal cells were identified by red fluorescence owing to Kaede color conversion on exposure to UV light. (B) Post-metamorphosis: The presence of neural cells is identified by red fluorescence and cells that have newly emerged after metamorphosis are identified by green fluorescence. (C) (B) Magnified image of the area within the frame.

Key Strains/Studies

We preserve approximately 130 lines, including various fluorescent protein-expressing lines, enhancer trap lines, cell cycle visualization FUCCI lines, and mutant lines. These transgenic and mutant lines are useful for molecular studies, and they are available from NBRP. In addition, approximately 350 types of reporter constructs and tissue-specific TALEN expression plasmids can also be provided.

● Tg[MiCiβ2TBK]2

This is a transgenic strain that expresses Kaede, a coral-derived fluorescent protein, in the nervous system. The color of the Kaede protein can be changed from green to red on exposure to ultraviolet light (photoconversion activity). Therefore, we can accurately mark specific cells at a certain time and to track subsequent changes in the cells. Studies using this strain have shown that many of the glial cells that is present in the larval central nervous system remain after metamorphosis and they form the adult central nervous system including neurons in it (Fig. 1, *Nature* 469: 525-528, 2011).

● Tg[MiCiPC2K]2

This strain is one of the Kaede transgenic lines. It expresses fluorescent proteins in all neurons throughout the body. Because it emits extremely bright fluorescence in neurons, this transgenic line is an optimal strain for observing neurons and their axon trajectory. A study using this strain described the whole nerve network in the adult body. By this information, we can estimate how *Ciona* nervous systems regulate downstream tissues and organs (Fig. 2, *PLoS One* 12: e0180227, 2017).

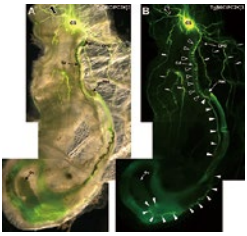


Fig. 2. Distribution of nerve cells in the sea squirt. (A) Kaede fluorescent label superimposed image of the dorsal side of a sea squirt and (B) Kaede fluorescent label image in the dark field. (From *PLoS One* 12: e0180227, 2017 Fig. 1A, B)

CORE FACILITY UPGRADING PROGRAM Drosophila

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Overview

Drosophila has a 110-year history as a life science research material. In addition to the ease of mass rearing and short life cycle, it has the following advantages: 1) The genome is compact compared with the complexity of the body plan such as formation of various tissues and organs. 2) Life phenomena at an individual level can be analyzed from the functions of genes/genomes. 3) Annotation of the genome sequence is accurate, and expression data of various genes in tissues and at developmental stage are accumulated. 4) Genetic engineering methods such as modified gene introduction and conditional regulation of the expression of such genes have been developed.

Drosophila melanogaster

Keeping ~ 100 adult flies in one bottle

This project aims to comprehensively preserve and manage genetic resources such as various *Drosophila* organisms and DNA clones, and provide them widely to the research community. The core facility, National Institute of Genetics and the sub-core facilities, Kyoto Institute of Technology and Kyorin University are responsible for collecting, preserving, and providing live resources. As a result of NBRP operations in the past 15 years of the three phases, this has become world's largest stock center. While fulfilling our international responsibilities, we aim to collect resources and improve quality in response to the demands. This contributes in accelerating the advanced research activities of the user community.

Wide variety of database groups that support *Drosophila* research

Key Strains/Studies

We maintain approximately 45,000 strains, including mutant strains, genome editing related strains (FlyCas9), RNA interference (RNAi) strains, spontaneous mutant strains of *Drosophila* wild species, and close relative of *Drosophila melanogaster*. We also have approximately 260,000 different cDNA, genome DNA clones, and Cas9 plasmids. The National Institute of Genetics collects, preserves, and provides RNAi and FlyCas 9 lines; Kyoto Institute of Technology is responsible for *Drosophila* wild strains, mutant strains, genetically modified strains, and cryopreservation of selected strains; and Kyorin University is in charge of wild, mutant and transgenic strains of closely related *Drosophila* species. In *Drosophila*, approximately 70% of the 13,936 protein coding genes have homology with human genes. In addition, gene networks are also conserved. Therefore, it has been widely used as a basic research material for diseases in recent years (*Nature* 542: 246-250, 2017). In addition, in species differentiation mechanisms such as lethality, infertility, and sex ratio skewness of interspecific hybrids with closely related species, elucidation by advanced research methods of *Drosophila* is expected (*Trends Genet* 33: 68-80, 2017). *Drosophila* is also an advanced research resource for proteome analysis (*Nature Genet* 38: 1440-1445, 2006).

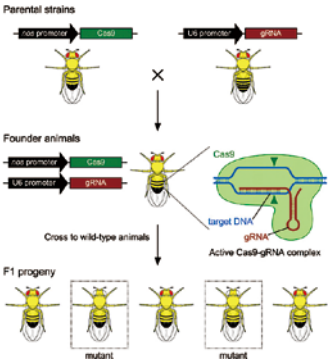

Fig. 1. Transgenic Cas9-gRNA system (From *Genetics* 195: 715-721, 2013 Fig. 1. Reprinted by permission of Oxford University Press on behalf of the Genetics Society of America.)

● y2 cho2 v1; attP40(nos-Cas9)/CyO (Cas-0001)

This is one of the transgenic lines that express Cas9 protein, and it is possible to create mutant lines with high efficiency (approximately 70%) by crossing with various guide RNA lines (Fig. 1, *Genetics* 195: 715-721, 2013).

CORE FACILITY UPGRADING PROGRAM Silkworms

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Overview

The silkworms (*Bombyx mori*) can not survive themselves without human support. It is a unique genetic resource in Japan as well as valuable resource in the world because it is maintained and preserved systematically as a strain only in Japan. Because of this background, a large number of natural mutants have been discovered and become the core of current NBRP silkworms. Among the stock, mutants have been discovered one after another that can be used as models of human genetic diseases. In addition, advances in silkworm genome analysis have led to the elucidation of genes involved in insect-specific functions such as food habit and preference (selection), resistance and susceptibility to viruses, fungi, and bacteria, and diapause. Because new pesticides are expected to be developed, it is a good insect model for controlling agricultural pests. Furthermore, there are no common diseases with humans, and breeding techniques are easy and inexpensive owing to the techniques developed through sericulture. Therefore, genetically modified silkworms are used for the production of useful substances (insect factories), and as an alternative animal for experimental animals for toxicity tests and drug screening.

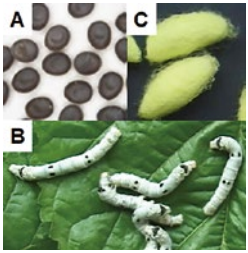

Fig. 1. Eggs (A), larvae (B), and pupae (cocoons) (C) of p50 standard strain

In this project, Kyushu University and Shinshu University collect, preserve, and provide living organisms. Gakushuin University collects, preserves, and provides DNA resources. In addition to providing services and support in terms of breeding methods and management techniques for researchers who have no breeding experience, we also supply silkworms for users involved in educational and cultural activities for silkworm users.

Key Strains/Studies

Kyushu University offers approximately 500 silkworm strains, including the p50 strain (Fig. 1), which is a standard strain used for genome information analysis. Shinshu University offers wild silkworms such as *Antheraea yamamai*, *A. pernyi*, and *Samia cynthia pryeri*. Gakushuin University provides more than 190,000 clones of genomic DNA libraries (Fosmid, BAC) and cDNA libraries of *B. mori* and related species.

● Recent topic reported in the *Zebra* mutant

The pattern of horizontal stripes found in the larvae of *Zebra* strains is also found in several Lepidopteran larvae and is used as a warning signal to predators (Fig. 2). Recently, it has been revealed that the gene responsible for the zebra trait is *Spz3*, one of the Spätzle family genes involved in the regulation of innate immunity in humans. In silkworms, as in humans, Spz3 signaling has been shown to induce zebra-stripe melanogenesis via Toll receptors (*PNAS* 114: 8336-8341, 2017).

Fig. 2. Zebra silkworm (top) and swallowtail butterfly (bottom) (From Fig. 1 of News "A part of the immune system was diverted to stripe pattern formation of insects?" Haruhiko Fujiwara, Graduate School of Frontier Sciences, The University of Tokyo)

● Survey and use for potential genetic variation

As a result of investigating the efficiency of protein production in recombinant baculovirus AcMNPV using luciferase assay for the NBRP resources, it became clear that the production efficiency differs greatly between strains, and that this involves the locus on silkworm chromosome 3. The use of nine strains showing high luciferase activity in this study is expected to dramatically improve the production efficiency of useful proteins such as pharmaceuticals (Fig. 3, *Appl Microbiol Biotechnol* 98: 3049-3058, 2014).

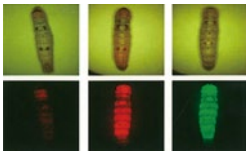

Fig. 3. Compared with general strains (left), in strains (middle and right) with high protein expression, strong fluorescence can be detected even when infected with recombinant viruses containing different fluorescent genes. (From the newsletter "Okaikosama" No. 40, 2018)

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Overview

C. elegans, having approximately 1,000 somatic cells, has various tissues that comprise the reproductive system, nervous system, muscle system, and digestive system and are functionally similar to those of higher animals, and cell lineage (path of differentiation from fertilized egg to adult in all cells) has been identified. In addition, the life cycle is approximately 3 days (life span is approximately 3 weeks), and almost 40% of genes encoding approximately 20,000 proteins have similar sequence and function to human genes. In addition, feeding RNA interference is available. Therefore, it is possible to efficiently inhibit gene expression simply by feeding the nematode with bacteria expressing double-stranded RNA that is complementary to the target gene.

In this project, the number of deletion mutants collected and released exceeds 8,000 by the 3rd phase. In the 4th phase, we will continue to find deletion mutants of each gene from the frozen stock of existing random mutants by whole genome sequencing to further expanding the deletion mutant resource. After purification, they are preserved, released, and provided to the applicants (Fig. 1). Furthermore, we also provide Cre recombinase transgenic strains that can be used as conditional knock-out tools and are effective for analysis of lethal mutants and fluorescence-labeled balancer strains that have been prepared based on recombination suppression within the same chromosome. These are expected to facilitate genetic analysis of *C. elegans*.

Caenorhabditis elegans

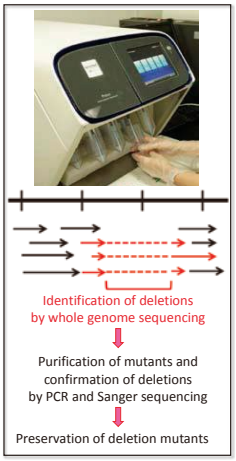

Fig. 1. Flow chart of the collection of deletion mutants

Key Strains/Studies

In addition to wild-type strains, approximately 11,100 various gene-deficient strains, 50 Cre recombinase transgenic strains, and 70 balancer strains are available.

● *lrk-1* (tm1898)

The nematode *lrk-1* gene is highly homologous to the human *LRKK2* gene, which is one of the causative genes for familial Parkinson's disease, and encodes a protein kinase. It is used in research on Parkinson's disease because it is useful for analyzing the molecular mechanism underlying neurodegenerative diseases (*J Neurosci* 37: 11085-11100, 2017).

● *pdf-1* (tm1996)

One of the leading fields of research using *C. elegans* is analysis of learning and memory. Conditioned nematodes under starvation and presence of salt exhibit learning behavior that avoids salt. However, males conditioned with hermaphrodite individuals under these conditions show salt-preferring motility to prioritize mating behavior (Fig. 2). This male-specific learning behavior involves Mystery Cells of the Male (MCM; Fig. 3), which is a male-specific interneuron derived from differentiated glia in a larval-stage male. The above-mentioned learning behavior has been found to be lost in the *pdf-1* gene mutant (tm1996), which is highly expressed in this cell (*Nature* 526, 385-390, 2015).

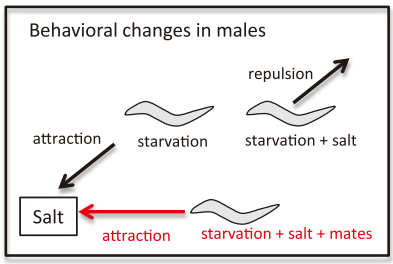

Fig. 2. Male-specific conditioned learning behavior

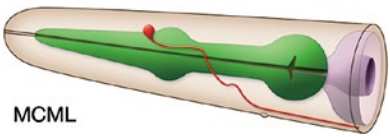

Fig.3. Diagram depicting the morphology and position of one of the bilateral pairs of MCM neurons in the head of a male worm. (From Wormatlas http://www.wormatlas.org)

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Overview

Arabidopsis thaliana is small in size, and it is possible to obtain the next generation of seeds in three months. In addition, related information and techniques such as complete genome sequence and an efficient protocol of transformation are also available. Therefore, it is widely used as a model plant in academic studies in Japan and other countries. Cultured plant cells have traditionally been the strength of Japan in terms of resources, and are expected to be used in a wide range of research from cell biology to production of useful substances.

Arabidopsis thaliana (top) and cultured plant cells (bottom)

The RIKEN BRC Experimental Plant Division collects, preserves, and provides cultured cells and DNA clones of model plants in addition to ecotypes (wild-type strains) and gene knocked out mutants of *Arabidopsis*. In the 4th phase of NBRP, we are working on the improvement of the catalogue database with aim of enhancing international awareness and user convenience of all these diverse resource groups. In addition, as a resource with the world's highest level of reliability, we are working on establishing a quality control system, to be able to respond to resources in which innovative technologies have been employed, such as mutants produced by genome editing. We are also working with all the other NBRP resource facilities to strengthen information dissemination to the research community and support plant research for solving environmental, food, and substance production issues.

Key Strains/Studies

In *A. thaliana*, in addition to mutant libraries of both gene disruption and gene over-expression, individual mutants and transgenic strains (~350 strains) are available. We also offer ecotype strains (~530 stocks) collected from all over the world. The *A. thaliana* full-length cDNA clone (RAFL clone) is a global standard resource including approximately 21,000 clones that have been entirely sequenced. We also provide TAC clones with inserted *A. thaliana* genomic fragments and ORF clones of transcriptional factors. In addition, approximately 320,000 cDNA clones derived from eight model plants are available. We are able to offer 66 plant cell lines (including transgenic lines expressing GFP) of model plants and medicinal plants, including *A. thaliana*.

● Bu5 (sja02900)

A. thaliana is found worldwide. Even within same species, there is a difference in osmotic tolerance. The Bu5 strain, which originates from the suburb of Goettingen in Germany, has remarkable osmotic pressure (water deficiency) resistance compared with the standard strain Col-0. It was found that the responsible gene *ACQOS* identified by mapping experiments is also an important gene for plant immune response. Therefore, similar to the Bu5 strain, *A. thaliana* lacking the *ACQOS* gene acquires high osmotic tolerance; however, its disease resistance decreases. In other words, it became clear that the presence or absence of the *ACQOS* gene is a decisive factor in disease resistance and osmotic resistance (Fig. 1, *Nat Plants* 3; 17072, 2017).

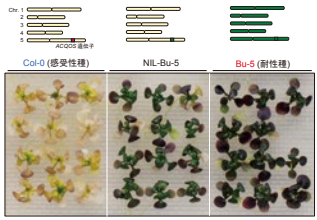

Fig. 1. Col-0 standard strain (left) dies under osmotic stress, but Bu5 strain (right) can survive. The standard strain in which *ACQOS* gene was replaced with Bu5 type (center) acquired osmotic tolerance. (*Nat Plants* 3; 17072, 2017)

● Tobacco BY-2 cultured cells (rpc00001)

This cell line is the typical cultured plant cells also known as "plant HeLa cells" because they grow rapidly. New gene involved in the biosynthesis of daurichromenic acid (DCA) with anti-HIV activity was isolated from *Rhododendron dauricum*. An experiment using tobacco BY-2 cultured cells has revealed that DCA is synthesized extracellularly (Fig. 2, *Plant Physiol* 174: 2213-2230, 2017).

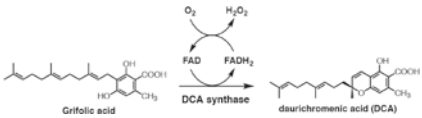

Fig. 2. DCA synthase catalyzes the conversion of grifolic acid to DCA using FAD and oxygen. This enzyme was confirmed to be a secretory protein using Tobacco BY-2 cells. (From the University of Toyama)

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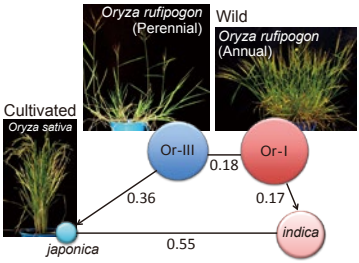
Overview

Rice is an essential food crop and is a plant that has evolved with the history of humanity. From breeding science to develop delicious and disaster resistant rice strains, to basic research, Japanese researchers have long been active in all fields related to studies in rice. Genetic resources of cultivated rice are said to be more than 140,000 strains in the world; in Japan, a total of more than 46,000 strains are preserved at the Ministry of Agriculture, Forestry and Fisheries, universities and research institutes.

Apart from these genetic resources, in NBRP-Rice, the National Institute of Genetics is in charge of collecting, preserving, and providing wild rice that is usually difficult to preserve, and Kyushu University collect, preserve, and provide experimental strains, such as mutant strains and strains with chromosome fragment substitution derived from wild rice. In the 4th phase of NBRP, to increase the added value of each strain, we are performing the following: evaluation of traits in rice, construction of molecular markers, reclassification of wild strains, and maintenance and development of integrated database (Oryzabase) including rice gene and genome information. In 2019, the operation of a cross-sectional data search system (PGR-Gateway) has been started in cooperation with the Genebank Project of National Agriculture and Food Research Organization (NARO), and now users can more efficiently access genetic information from both resources.



Genetic distance (number) between cultivated rice and their wild ancestors and size of intragroup variation (circle size)

Key Strains/Studies

We can provide approximately 19,000 lines, including wild strains, experimental strains derived from wild strains, MNU mutant strains with different genetic backgrounds such as Kin-maze, TC65, Kita-ake, and Yuki-hikari, and chromosomal segment substitution strains in which a chromosome derived from closely related wild species, such as *Oryza glaberrima*, *O. meridionalis*, *O. glumaepatula*, *O. sativa indica*, and *O. sativa japonica*, are introduced into cultivated rice.

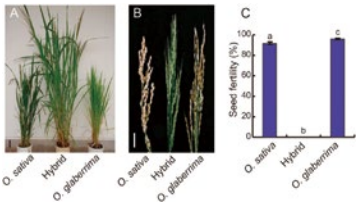


Fig. 1. In crosses between African and Asian cultivars, spikelets develop but are sterile. (From *PNAS* 115: E1955-E1962, 2018 Fig. 1)

● *Oryza glaberrima* chromosomal segments substitution strain

The African cultivar (*O. glaberrima*) has a resistant gene against unfavorable environment such as high temperature, which is not found in Asian cultivar (*O. sativa*). Because it becomes sterile in crosses between both varieties, it has been difficult to search for useful genes by hybrid cross experiments. Heavy-ion beam mutagenesis was performed in hybrid seeds between a chromosomal segment substitution strain containing S1 locus region involved in sterility and an Asian cultivar strain. Consequently, individuals in which fertility was reversed were generated and the causative gene was found to be SSP gene (Fig. 1, *PNAS* 115: E1955-E1962, 2018).

● MNU mutagenized strain *drp7* (SG1105) in Kin-maze strain

Because the leaf surface of rice is hydrophobic, it helps the plant in maintaining gas exchange with the outside under water. The MNU-induced mutant line *drp7* cannot maintain the air layer in water, and has a reduced number of wax platelets in the cuticular layer on the leaf surface and reduced levels of hydrophobicity and photosynthetic ability in water. In addition, in the wax composition on the leaf surface, the amount of C30 primary alcohols decreases and the amount of C30 aldehydes increases. Thus, the causative gene *Leaf Gas Film 1* (*LGF1*) identified by linkage analysis was found to be involved in C30 primary alcohol synthesis (Fig. 2, *New Phytol* 218: 1558-1569, 2018).

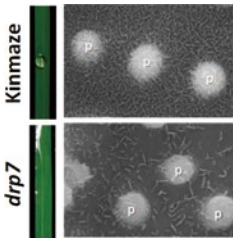


Fig. 2. Decrease in hydrophobicity of leaf surface one day after flooding (left) and decrease in the number of epicuticular wax platelet (right) under an electron microscope in *drp7* strain (bottom) (right: P = papillary projections; from *New Phytol* 218: 1558-1569, 2018 Fig 1 with modifications)

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Overview

Wheat is one of the world's three major crops. Wheat consists of diploid Einkorn wheat (2n = 14), tetraploid Emmer wheat (2n = 28), and hexaploid common wheat (2n = 42). Bread wheat, which is the most important staple of our diet, is an allohexaploid having three different genomes A, B, and D in one nucleus. The A genome is derived from a wild diploid wheat *Triticum urartu*, and other two genomes are from related wild weed species in the genus *Aegilops*. Such complexity of the genomic structure has been a major obstacle to whole genome sequencing of bread wheat. Recently, we successfully completed decoding the genome sequence under the initiative of the International Wheat Genome Sequencing Consortium (IWGSC) (*Science* 361: eaar7191, 2018). The core facility of NBRP-Wheat, Graduate School of Agriculture, Kyoto University, took part of the IWGSC. We prospect that various molecular studies in wheat will be promoted.

The complete sequence of the bread wheat genome was published in the August 17, 2018 issue of Science.

While most gene banks in the world are focusing on collection of modern cultivars of wheat, NBRP-Wheat collects, preserves, propagate, and provides wild relatives and landraces of wheat. With the completion of genome sequencing, the collections of NBRP-Wheat will be more accessible for research activities. We hope NBRP-Wheat can be regarded as one of the centers of global wheat genetic resources. In the 4th phase of NBRP, we will develop new resources and various core collections for genetic analysis. Next, we will make the resource database KOMUGI more attractive by accumulating phenotypic and genotypic data. We have started to collaborate with other gene banks in the world. One of the domestic cooperation is with the National Agriculture and Food Research Organization (NARO) Genebank, which resulted in a cross-sectional data search system (PGR-Gateway).

Key Strains/Studies

We mainly supply wild species and landraces of wheat (~6,700) and related species in the *Aegilops* and *Secale* genera (~4,200). In addition, we provide experimental strains, including Chinese Spring, a genetic standard cultivar of hexaploid wheat used for determination of the reference genome sequence. The experimental strains (~1,600 lines) include mutants, recombinant inbred lines, chromosome substitution lines, synthetic polyploids, aneuploids, alien chromosome addition/substitution lines, and other genetic strains. We terminated distribution of DNA resources at the end of the 3rd phase.

● Cultivar Chinese Spring (abbreviated as CS, LPGKU 2269), the standard cultivar of genetics and genomics of bread wheat, and Cultivar Norin 61 (abbreviated as N61, LPGKU 2305), the representative modern wheat cultivar in east Asia

The bread wheat cultivar CS is the material of decoding the reference genome sequence of hexaploid wheat. CS has been used in many research activities as the standard for many years. This is the reason why many aneuploid, chromosome deletion lines and substitution lines were created based on CS. These are stored in NBRP-Wheat. Now with the genome sequence in hand, we expect the experimental strains of CS to be actively used as research materials again.

As the first step of comparative genome analyses, we, the International wheat 10+ Genome Project, have practiced *de novo* assembly of 15 world leading hexaploid wheat varieties (*Nature* 588: 277–283, 2020; Fig. 1). The Japanese team was in charge of the genome sequencing of the cultivar N61 that are currently being used in many different post-genome studies.

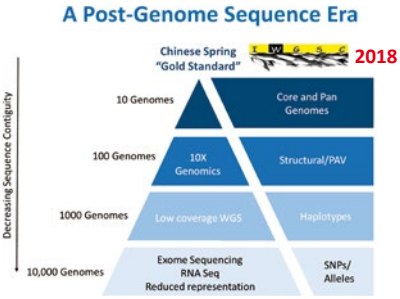

Fig. 1. Outline of wheat research in post-genomic era
It has been proposed to promote wheat sciences by determining the genomic sequence (or partial sequence) at different levels according to the research goals. The cultivar Norin 61 in the NBRP-Wheat was selected as one of the 10 wheat genomes for *de novo* sequencing, and its assembly has been completed.

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Overview

Barley is used for brewing, food, and feed, and is important as a functional food and feed with high nutritional value. There are a variety of wild and cultivated species that have the greatest wide adaptability (from Alaska to India), excluding the tropics, and resistance to environmental changes such as drought, salt, and moisture damage. In addition, because it is a diploid, it is easy to detect mutations and high quality genome assemblies have been completed (*Nature* 588: 284-289, 2020). It is used as a model plant for applying the results of plant science including the identification of useful genes.

Diversity in barley spikes

The core facility of NBRP-Barley, Institute of Plant Science and Resources, Okayama University, preserves the barley strains that have been collected and developed independently, and is one of the world's five best barley resource centers in East Asia. In the 4th phase of NBRP, the Barley DB has been updated and integrated with high-density transcript maps and SNP information based on cDNA sequences, including characterization of each strain, and will contribute to the genome and gene analysis of barley and related plants, and finally the development of new cultivars.

Key Strains/Studies

In addition to the standard genome analysis line "Haruna Nijo", it is possible to supply about 5,300 cultivated barleys, wild species, experimental lines, and a core collection of 380 strain. The core collection is a series of strains that are selected to maximize the genetic diversity of barley and improve the accessibility in genetic analysis and breeding. We also offer full-length cDNA clones of barley (Haruna Nijo: 5,000 clones) and BAC clones (Haruna Nijo: 300,000 clones, wild barley: 180,000 clones).

● Barley Core Collection and Barley BAC Library

The reduced seed dormancy period acquired during the process of barley cultivation by human has led to the emergence of pre-harvest sprouting (phenomenon of sprouting of grains on spikes) due to the high moisture condition in Japan and Northern Europe where there is a lot of rain during the harvesting period (Fig. 1). The results of genetic linkage analysis using strains with different lengths of seed dormancy and BAC clone sequencing analysis indicated that the responsible locus *Qsd1* was shown to encode alanine aminotransferase (AlaAT). Furthermore, the evolutional analysis of *AlaAT* gene sequences using the barley core collection showed that wild barley near Israel (south Levant) was the origin of barley for brewing (varieties with short dormancy) and varieties with mutations imparting shorter dormancy were selected from these during malt production for beer, and were dispersed to various parts of the world (*Nat Commun* 7: 11625, 2016).

Fig. 1. Germination after 5 weeks of barley strains that differ only in the dormant (left) and non-dormant (right) allele (From *Nat Commun* 7: 11625, 2016 Fig. 1).

● Turkey 45 (T615), H.E.S.4 (I622), Maja (U053), and Sirius O.525 (U121)

Fusarium fungi that cause head blight produce toxins that are mixed into food and livestock feeds and have a harmful effect on the human body. Comparative analysis of the metabolites of *Fusarium* blight-resistant (Maja · Sirius O.525) and susceptible strains (Turkey 45 · H.E.S.4) showed that nicotinamide mononucleotide (NMN), a metabolite related to nicotinamide mononucleotide adenyltransferase (NMNAT), was found to function as an inducer of plant resistance (Fig. 2, *Sci Rep* 7: 6389, 2017).

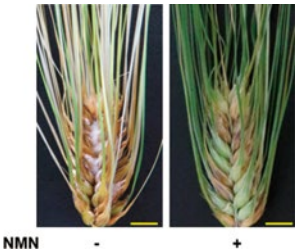

Fig. 2. Symptoms one week after inoculation of NMN-treated (+: right) and untreated (-: left) barley spikes with *Fusarium graminearum* (From *Sci Rep* 7: 6389, 2017 Fig. 5a)

CORE FACILITY UPGRADING PROGRAM Lotus / Glycine

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URL : https://www.legumebase.brc.miyazaki-u.ac.jp/

Overview

Leguminous plants are extremely important species that inhabit diverse environments from tropical to temperate regions, and are used for various purposes, including food. In addition, they have unique characteristics, such as diversity of seed storage proteins and symbiosis with rhizobia and mycorrhizal fungi that have the ability to fix nitrogen. Japanese trefoil (*Lotus japonicus*) is a wild perennial legume native to Japan and has a short life cycle (2–3 months). Since the genome sequence of *Lotus japonicus* was decoded, its use has been rapidly increasing in the field of basic research as a leguminous plant model. Alternatively, soybean (*Glycine max*) contains several proteins in its seeds, and also has many functional chemical components such as isoflavones, saponins, and proteins (peptides). Therefore, as one of the most important leguminous crop in the world, several basic research studies have been accumulated.

In the 4th phase of NBRP, the *Lotus/Glycine* core facility in the University of Miyazaki comprehensively collects, maintains, and provides live and DNA resources of Japanese trefoil and soybean. The sub-core facility in Tohoku University is in charge of rebuilding LegumeBase, an integrated database for searching and providing Japanese trefoil and soybean strains. The two institutes coordinate to add characteristic information such as contents of seed components and morphogenesis of each strain, and to provide functional information to users along with high-quality resource maintenance.

Japanese trefoil life cycle (seed, 1-month-old plant, flower, ripening pod). Upper right: Root culture system derived from *Lotus corniculatus*. Bottom: soybean [flower (bud), ripening pod, seeds of various soybean varieties].

Key Strains/Studies

We offer approximately 1,500 germplasm accessions of Japanese trefoil (*Lotus japonicus*), including wild accessions, various experimental strains, retrotransposon tag strains (LORE1), EMS (ethyl methanesulfonate)-induced mutant strains, and EMS-M2 bulk seeds. In addition, approximately 6,700 STM (Signature Tagged Mutagenesis) strains of root nodule bacteria and a root culture system (super root) derived from *Lotus corniculatus* has been conserved and can be provided. Furthermore, we can provide from our stock of approximately 1,000 soybean cell lines, including the original wild *Glycine soja* strains and cultivar for green soybean, as well as mutant strains and EMS-M2 bulk seeds. Available DNA resources include BAC and TAC clones (~27,000), cDNA clones (~160,000) in Japanese trefoil, and full-length cDNA clones (~38,000) of soybean. We also offer Japanese trefoil rhizobia DNA-plasmid clones (~4,200) and soybean rhizobia BAC and cosmid clones (~8,700).

● *Lotus japonicus* wild accessions

Genome analysis and cultivation experiments of 136 Japanese *L. japonicus* wild accessions revealed that *L. japonicus* settled in Kyushu about 20,000 years ago and then spread throughout Japan. Furthermore, it was found that genes related to overwintering and flowering played an important role in the adaptation of *L. japonicus* in the northern region of Japan (Fig.1, *Nat Commun* 11: 253, 2020).

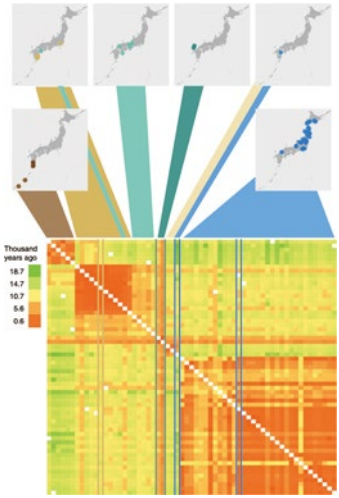

Fig 1. The upper map shows the collection site of *L. japonicus* in Japan. The lower panel shows a heatmap of divergence times (years ago) for pseudodiploid pairs as estimated from the PSMC analysis. The estimated divergence times for all pairs of accessions showed clear clustering along the inferred colonization route with Southern and Northern Japan having last contact 10–18 thousand years ago, consistent with colonization after the last ice age. Tsushima Island may represent a point of origin for all of the Japanese *Lotus* populations (From *Nat Commun* 11: 253, 2020 Fig. 1).

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Overview

Many Solanaceae family plants are vegetables, and are evolutionarily distant from *Arabidopsis thaliana* (Brassicaceae family) and *Lotus japonicus* (Legumiaceae family), which are advanced in resource development and maintenance among dicotyledonous plants. Among Solanaceous plants, tomato is the most widely produced fruit vegetable in the world and contains several functional ingredients that are important for health maintenance. Conversely, the genome size is relatively small (950 Mbp), the genome sequence has been decoded, and it has many features not found in conventional model plants (such as fruit development and neutral photoperiod response). Among these, tomato is also important as a model plant to study Solanaceous plants and fruit development.

A model cultivar, Micro-Tom Japan

At NBRP-Tomato, the core facility, University of Tsukuba and the sub-core facility, Osaka Prefecture University are in charge of collecting, preserving, and providing live resources and DNA clones, respectively. The other sub-facility, Meiji University is in charge of constructing and managing various DNA information databases (TOMATOMICS). The dwarf tomato cultivar Micro-Tom Japan has advantages as an experimental plant (small size, short life cycle, growable with weak light, genome sequence decoded, and Agrobacterium-mediated transformation). In the 4th phase of NBRP, we will prepare resources based on Micro-Tom Japan and its variants, and add genome sequences and trait characteristics information. Through this, we will achieve high quality and strive to further promote resource utilization.

Key Strains/Studies

Approximately 2,200 strains, including wild and cultivated strains, T-DNA tag strains of Micro-Tom Japan, and EMS and gamma ray mutagenized strains (including their M3 bulk seed set), are distributed through the TOMATOMA database. Micro-Tom cDNA clones derived from fruits, leaves and roots are distributed through the omics database for tomato TOMATOMICS. The information provided by TOMATOMICS includes sequence information of approximately 36,000 ESTs and approximately 13,000 full-length cDNAs.

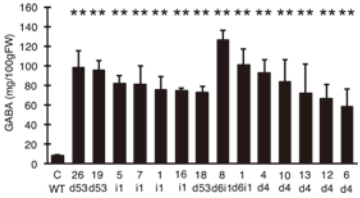

Fig. 1. Comparison of GABA concentrations in fruits of T1 generation individuals of *SlGAD3* gene modification lines, which is one of the *GAD* genes, of the flowering type (left corner) (From *Sci Rep* 7: 7057, 2017 Fig. 5)

● Micro-Tom (MT-J) (TOMJPF00001)

GABA, which is abundant in tomatoes, is noted for its suppressive effect on blood pressure elevation, and further stable and high accumulation strains are required. Therefore, we attempted to increase GABA accumulation by deleting the autoinhibitory domain of GABA biosynthetic enzyme (GAD) gene using the CRISRP-Cas9 system. Consequently, the accumulation of GABA in the fruit increased 7–10 times without decreasing the flowering rate and fruit yield (Fig. 1, *Sci Rep* 7: 7057, 2017).

● EMS treatment derived mutant (TOMJPE2753-1)

Parthenocarpy, a property to produce fruit without pollen, is an important trait for tomato, which is cultivated year-round. procera (*pro*) strain with a loss-of-function mutation at the *SlDELLA* locus exhibits parthenocarpy; however, it has problems with fruit traits. One of the EMS-induced mutant strains, TOMJPE2753-1 (*pro-2*), has a reduction-of-function mutation at the *SlDELLA* locus, and while retaining parthenocarpy, the problematic traits found in the *pro* strain are also improved. As this strain maintains high yield in the summer season, further research is expected on causality between heat resistance and parthenocarpy (Fig. 2, *Sci Rep* 8: 12043, 2018).

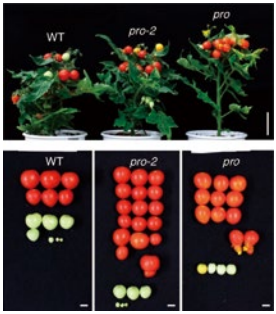

Fig. 2. Comparison of plant and fruit phenotypes of wild type (left), *pro-2* (middle), and *pro* (right) strains grown in greenhouse in summer (From *Sci Rep* 8: 12043, 2018 Fig. 6b, c)

Chrysanthemum

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Overview

The family *Asteraceae* is one of the most prosperous plant groups, containing more than 23,000 species. Among them, the *Chrysanthemum* genus and its closely related genera (*Chrysanthemum sensu lato*) have undergone characteristic evolution with polyploidization and hybridization. Cultivated chrysanthemum (*C. morifolium*) is one of the three major flower plants in the world. It is an industrially important species that accounts for one-third of cut flower production in Japan. *Chrysanthemum sensu lato* also includes many species that produce various pharmacologically active secondary metabolites, such as the *Artemisia* species.

Various chrysanthemum plants and their relatives.

NBRP-Chrysanthemum collects, preserves, and provides the world's largest number of strains of the *Chrysanthemum* genus distributed in the East Asia region. The self-incompatibility (property of producing no seeds after self-pollination) and hyperpolyploidy found in the *Chrysanthemum* genus, are major obstacles in conducting genetic research, including developing inbred strains and breeding of cultivated varieties. The self-compatible mutant strain of a wild diploid species *C. seticuspe*, AEV2, which is the core facility of the NBRP-Chrysanthemum isolated by Hiroshima University, is extremely useful for overcoming these obstacles. In the 4th phase of NBRP, whole genome sequence and gene expression information of Gojo-0 line (Fig. 1), which has been established by repeating selfing of AEV2 stain, will be added. This makes it a better reference resource for cultivated chrysanthemums. Consequently, we will establish a molecular genetic research platform for the study of plants in *Chrysanthemum sensu lato*.

Fig. 1. The model strain in the genus *Chrysanthemum* Gojo-0

Key Strains/Studies

Focusing on the *Chrysanthemum* genus, we provide approximately 500 wild strains and approximately 60 experimental strains such as *C. seticuspe* inbred lines and interspecies hybrids.

● XMRS10

A draft sequence of the entire genome was determined for XMRS10, a semi-pure strain derived from AEV2. The analysis of this strain revealed that *C. seticuspe* has a genome size of approximately 3 Gbp and approximately 70,000 genes. In addition, sunflower and chrysanthemum were considered to have differentiated approximately 46 million years ago (Fig. 2, *DNA Res* 26: 195-203, 2019). Controlling the flowering time of the *Chrysanthemum* genus is important in the industrial world. A common feature of the *Asteraceae* family is that a large number of small flowers combine to form one flower-like structure (capitulum). As all genetic information has been decoded, it is hoped that research on such characteristics will be further advanced, and at the same time, breeding of cultivated varieties will be more efficient. Sequence information is publicly available from Mum Garden (http://mum-garden.kazusa.or.jp/), and can be used for gene function analysis in the broad-sense chrysanthemum plants using BLAST search.

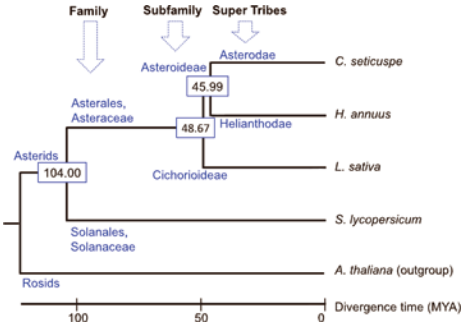

Fig. 2. A phylogenetic tree based on the 2,280 common single-copy genes of the four *Asterids* species and *A. thaliana*. (From *DNA Res* 26: 195-203, 2019 Fig. 4)

Morning glory

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Overview

The Japanese morning glory (*Ipomoea nil*) is a bioresource that was developed in Japan along with more than a century of knowledge amassed from its applications in genetics, physiology, natural product chemistry, and other research fields. It has several strong advantages for various areas of plant science, such as its highly homogeneous genome, which is the result of its high selfing rate and its restricted origin, as well as various mutants related to flower color and morphology induced by its highly active transposons. It is also an excellent model for plant physiology such as photoperiodic flowering, because it has high photoperiod sensitivity. Moreover, near-complete genome sequences of the Japanese morning glory were published in 2016 (*Nat Commun* 7, 13295, 2016). It is expected to grow in importance for its usefulness in applied research, including its use in ornamental horticulture, and its use as a model organism for the sweet potato, which is a member of the same genus.

Examples of mutants with a variety of flower colors, patterns, and morphology.

NBRP-Morning glory collects, preserves, and provides live and DNA resources through its core facility, Kyushu University and the sub-core facility, National Institute for Basic Biology. In the 4th phase of NBRP, to increase added value of our resources, we will enhance the integrated database of strain characteristic information and genomic information, and support it to develop as a Japan's leading bioresources.

Key Strains/Studies

Most of the mutant strains maintained in the NBRP originate from the late Edo period, and transposons of the *Tpn1* family are mutagens. In addition to these, we provide approximately 3,000 strains, including recombinant inbred strains and strains from natural populations worldwide and *Ipomoea* species. The DNA resources include BAC libraries comprising approximately 100,000 clones of Tokyo Kokei Standard strains, cDNA libraries comprising approximately 60,000 EST clones, and petal-specific expression vectors.

Fig. 1. Life extension of petals of *EPH1* knockdown strain (From *Plant J* 79: 1044-1051, 2014 Fig. 1a).

● Violet: Q0079

Suppression for petal senescence is an important floricultural trait that helps to preserve the vase life of cut flowers. Violet is extremely sensitive to short-day photoperiod, and reproducible transformation conditions have also been established. In the knockdown (RNAi) strain of the *EPHEMERAL1* (*EPH1*) gene, which is a member of NAC transcription factor family involved in leaf aging, the lifespan of morning glory petals was doubled (Fig. 1, *Plant J* 79: 1044-1051, 2014). A similar phenotype was also observed in strains in which the *EPH1* gene mutation was introduced by the CRISPR-Cas9 system (*Plant Physiol Biochem* 131: 53-57, 2018).

● Tokyo Kokei Standard strain (TKS: Q1065) and 19 strains of dwarf mutant *contracted* (*ct*)

Tokyo Kokei Standard strain is highly inbred, and the transposition of endogenous transposon is also suppressed. The *ct* mutant has small cotyledons and leaves with thick and dark green mesophyll. After completion of genome sequencing of Tokyo Kokei Standard strain, genetic linkage map and the physical map were integrated. This has revealed that the *ct* allele phenotype is due to the suppression of gene expression by a transposon inserted in the *CYP90C1* gene, which is involved in the biosynthesis of brassinosteroids (a group of plant hormones that promote elongation growth) (Fig. 2, *Nat Commun* 7, 13295, 2016).

Fig. 2. The *ct* strains of the three different alleles and wild-type (TKS) strain at 8 days of seeding (From *Nat Commun* 7, 13295, 2016 Fig. 3a)

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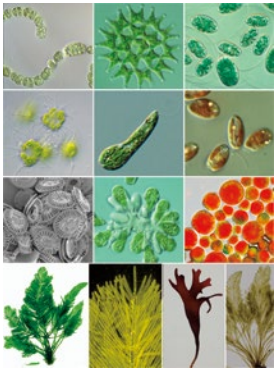
http://mcc.nies.go.jp/ (microalgae; NIES)
http://ku-macc.nbrp.jp/ (macroalgae; Kobe Univ.)

Overview



A wide variety of algal resources

"Algae" is a generic term for organisms that perform oxygen-producing photosynthesis, which exclude land plants but include a wide range of organisms such as prokaryotes, protists, and plants. Algae inhabit not only ordinary water environments but also extreme environments such as hot springs. Particular algal species also occur in areas with arid conditions, high salinity, and ice. Therefore, they are expected to have diverse biological functions. Consequently, algae are used in a wide range of fields, including those focused on research on evolution, photosynthesis and metabolic functions, energy, drug development, and environmental issues.

In NBRP-Algae, the National Institute for Environmental Studies and Kobe University collect, preserve, and provide microalgal strains and seaweed strains, respectively. Hokkaido University is involved in backup of important strains. In the 4th phase of NBRP, three institutions collaborated with each other for establishing a quality control system and collecting new important strains such as genome-analyzed strains and model organism candidate strains. Additionally, to increase the values of algal resources, we collected novel and useful information on strains, including morphology, photosynthetic pigment data, fatty acid composition, genomic information, and so on. We then upload all the data collected on our homepages to make them available to the world. We strive to provide the world's highest level of algal resources.

Key Strains/Studies

At present, we provide 4,139 strains belonging to 1,399 species (21 phyla, 64 classes, and 644 genera as of April 2021). We have a variety of species and strains, including model organisms for photosynthesis, cell division and evolutional researches from various aspects, phylogenetically and taxonomically important species, harmful species causing environmental problems, test strains for bioassay, and strains producing biomass or other useful substances, used in various research fields.

● *Chlamydomonas eustigma* (NIES-2499)

To elucidate the environmental adaptation mechanism of algae found in strong acidic environments, a comparative genomic analysis was performed between *C. eustigma*, an acidophilic species, and its related species, *C. reinhardtii*, a neutrophilic species. Consequently, their characteristic genes and metabolic pathways became clear because of the following reasons: increased expression of heat shock proteins and cell membrane proton ATPase, disappearance of fermentation (organic acid production) genes, acquisition of phosphagen kinase–amidinotransferase energy shuttle buffer system by horizontal gene transfer, and duplication of arsenic detoxification gene (Fig. 1, *PNAS* 114: E8304–E8313, 2017).

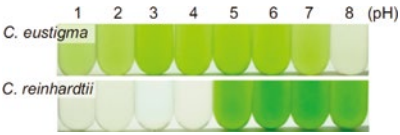


Fig. 1. Comparison of the growth ability of the acidophilic *Chlamydomonas eustigma* strain (top) and the neutrophilic *C. reinhardtii* strain (bottom) in culture for 24 h under various acidic conditions (*PNAS* 114: E8304–E8313, 2017, Fig. 1c).

● *Volvox rousseletii* (NIES-4029)

Volvox species are green, multicellular organisms comprising a large number of cells with flagella. Each cell is functionally differentiated, and an individual shows a harmonious photoresponsive behavior; however, its molecular mechanisms remain unknown. Using the zombie *Volvox* method which removes the entire cell membrane of *V. rousseletii*, it has become clear that the front and rear flagella of the organism share roles of steering and driving force via calcium ions (Fig. 2, *PNAS* 115: E1061–E1068, 2018).

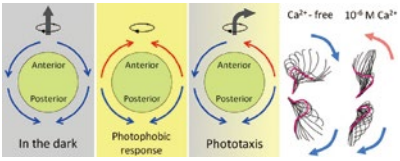


Fig. 2. The direction of the water flow by the front and back flagella under different light conditions (left) and change in movement of the front and back flagella in the presence or absence of calcium ions by the zombie *Volvox* method (right) ("*Volvox*'s flagella discovered to be functionally differentiated-revealed by zombie *Volvox* experiment", Tokyo Institute of Technology Press Release, with modifications).

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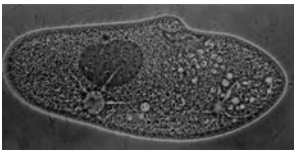
Overview

The *Paramecium* genus is a group of protists belonging to the *Ciliophora* phylum. They are large (150-300 μm) among unicellular organisms and easy to culture or manipulate under a microscope; therefore, they are used as model organism of eukaryotic cells for various basic researches (such as endosymbiosis, intermediate host of pathogenic bacteria, infection prevention, aging, ciliary movement, binucleation, sexual cell recognition, conjugation, deviated codons, phagocytosis, circadian clock, osmotic pressure control, environmental adaptation, taxis, ion channels, learning, and water purification). In addition, genome sequences of macronuclei (vegetative nuclei) have been decoded in several species (*Nature* 444: 171-178, 2006; *Genetics* 197: 1417-1428, 2014), and various genetic approaches have been developed.



A phase contrast microscope image of a *P. caudatum*

Yamaguchi University, the core facility of NBRP-*Paramecium*, preserves and provides 24 species which are the largest number in the world. In the 4th phase of NBRP, we aim to develop high-quality *Paramecium* resources that will become an international standard, while providing stable supply through the development of cryopreservation technology and adding each strains' information such as syngen (conjugable isogenic population), mating type (sex), collection site, and phenotypic characteristics. We are also working to disseminate research using *Paramecium* resources by providing the strains with their endosymbiotic bacteria or algae, and holding exhibitions and technical workshops.

Key Strains/Studies

Although more than 50 *Paramecium* species are stated, only 34 species are still collectable. NBRP-*Paramecium* has stored 24 species (~900 strains) and is ready to provide 9 of them (~40 strains) immediately.. We also accept to consultation on the provision of a variety of monoclonal antibodies against *Paramecium* species and their endosymbionts. Please consult us regarding the use of these antibodies.

● Ai253 (*Paramecium caudatum* PC121100A)

Ciliates such as *Paramecium* genus have a property of gathering at the interface of a solid with sufficient nutrient sources and stable environment. The behavior of *P. caudatum* near the wall surface (solid-liquid interface) was analyzed by fluid dynamics simulation. We found that the duration of sliding behavior in the vicinity of the wall surface can be explained only by two factors: Cell shape (elliptical shape) and reduction of propulsive force (characteristics of mechanical stimulus response) due to the decreased movement of cilia on the wall contact side (Fig. 1, *Commun Integr Biol* 11: e1506666, 2018).

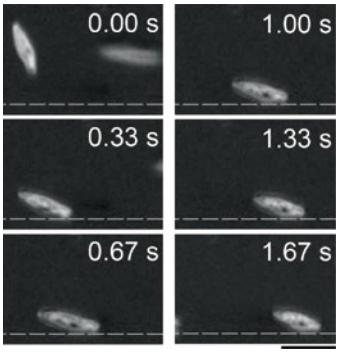


Fig. 1. Sliding behavior of *P. caudatum* on solid surface (dashed line). Bar (lower right) = 200 μm. (From *Commun Integr Biol* 11: e1506666, 2018 Fig. 1B with modifications)

● Yad1g1N (*Paramecium bursaria* PB031010B) and Yad1w (*P. bursaria* PB031012B)

P. bursaria has symbiotic *Chlorella* species within a cell (secondary symbiosis: endosymbiosis between eukaryotic cells) (Fig. 2). A comprehensive gene expression analysis was conducted by the RNA-Seq between the Yad1g1N, which is a strain with symbiotic *Chlorella* species, and Yad1w, which is a strain without the symbiotic algae. Consequently, we found that the expression levels were different for 6,698 genes out of the 10,557 genes identified. They included genes encoding stress response proteins and genes with the antioxidant activity (*BMC Genomics* 15: 183, 2014). Elucidation of the secondary symbiosis mechanism using these strains is still ongoing (*Symbiosis* 71: 47-55, 2017; *Symbiosis* 75, 51-59, 2018).

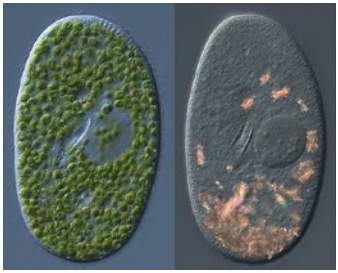


Fig. 2. *P. bursaria* cells with (left) and without (right) symbiotic *Chlorella cells*.

Cellular slime molds

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Overview

Dictyostelia, known as cellular slime mold, is unicellular amoebae that feed on bacteria and proliferate by fission. One of their key features is that when they are placed under starvation stress, they aggregate to form multicellular structures that develop into fruiting bodies composed of spore balls, or sorus, and supporting stalks (Fig. 1). Experimental strains, such as AX2, can be grown axenically and genetically modified. Their whole genome sequence data and various expression vectors are also available. Therefore, cellular slime molds are used as a model organism in basic science fields such as cell biology, developmental biology, biophysics, and mathematical biology. They are also used in the fields of medical science and drug discovery as infection hosts for pathogenic bacteria and organisms producing useful physiologically active substances. Recently, similar to *E. coli* and yeasts, cellular slime molds are used as a working platform for molecular biology experiments and as an experimental system for evaluation.

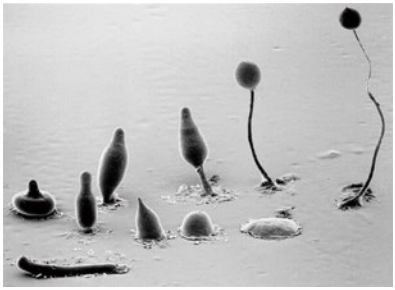

Fig. 1. Life cycle of *Dictyostelium discoideum* (photograph taken with scanning microscope; from DictyBase photo collection). Right: fruiting body, Lower left: slug.

In NBRP-Cellular slime molds, the core facility, RIKEN Center for Biosystems Dynamics Research (BDR) collects, preserves, and provides of strains and DNA resources. The sub-core facility, University of Tsukuba, conducts training courses in addition to the preservation of these resources. In the 4th phase of NBRP, we will develop high-quality resources that become international standards and add characteristic information of each strain. In addition, we are promoting public relations such as displaying actual cellular slime molds and issuing newsletters to increase new users.

Key Strains/Studies

We can provide four groups of wild strains (*parvisporids* · *heterostelids* · *rhizostelids* · *dictyostelids*) and mutant strains (~1,100 strains) mainly of *Dictyostelium discoideum*. We also provide expression vectors, gene knock-out constructs, and plasmid vectors (~420 clones), including All in one CRISPR-Cas9 vector (*Sci Rep* 8: 8471, 2018).

● Ax2 (*D. discoideum* S00001)

Left-right asymmetry is a basic feature of body plan. It has been suggested to be attributable to the chirality of cells. We analyzed the movement of cellular slime molds using newly developed Riesz Transform Differential Interference Contrast Microscopy (RT-DIC). Consequently, we found that the cells tend to move clockwise on a two-dimensional substrate, and the radially extending cell protrusions tend to rotate right-spirally in a three-dimensional substrate (Fig. 2, *Nat Commun* 8: 2194, 2017).

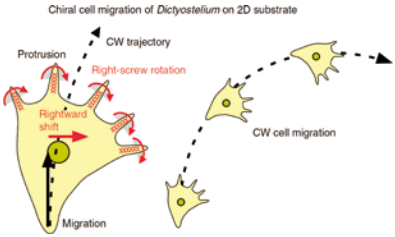

Fig. 2. Schematic diagram of the clockwise motion of cellular slime molds on 3D and 2D substrates (From *Nat Commun* 8: 2194, 2017 Fig. 8d)

● KAx3 (*D. discoideum* S00184)

In the soil, single-celled cellular slime molds are preyed by nonparasitic nematodes. However, they escape from predation by forming fruiting bodies. Accordingly, we investigated the response and effects of the cellular slime molds against *Meidogyne incognita*, one of the root-knot nematodes infesting and damaging many plants, including grains. Consequently, we have found that chemicals released from fruiting bodies have a repelling effect that is potent enough to protect plant roots from *M. incognita* (Fig. 3, *PLoS One* 13: e0204671, 2018).

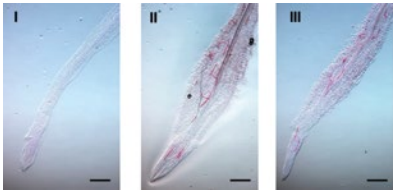

Fig. 3. Preventive effect of extracts from the fruiting bodies of cellular slime molds on infestation of *Lotus japonicus* roots with root-knot nematodes (red). Distance from the cellular slime mold fruiting body extract is closer in the order of I to III. (From *PLoS One* 13: e0204671, 2018 Fig. 5b)

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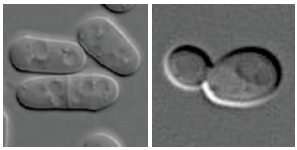
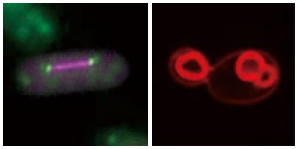
Overview

Yeast is an important eukaryotic model organism. Particularly, for *Schizosaccharomyces pombe*, a fission yeast, and *Saccharomyces cerevisiae*, a budding yeast, various experimental methods and research resources for genetic, biochemical, and molecular biology studies have been developed, including recombinant DNA technology. There are several examples of mechanisms that have been elucidated based on yeast research, such as cell cycle, intracellular protein transport, and autophagy. In addition, yeast is the first eukaryotic organism for which the genome project was completed. It has rich databases of genome, transcriptome, proteome, and other omics information, and plays a leading role in post-genome research. Alternatively, applied studies are also actively conducted in brewing and fermentation industries.



Fission yeast Budding yeast



Visualization of the nuclear division (fission yeast) Visualization of the vacuolar membrane (budding yeast)

In NBRP-Yeast/YGRC (Yeast Genetic Resource Center), the core facility, Osaka City University and the sub-core facility, Hiroshima Institute of Technology collect preserve, and provide various resources of fission yeast and budding yeast, respectively. The other sub-core facility, Hiroshima University is in charge of backing up the above resources. Through these activities, YGRC has become one of the top international yeast resource centers. In the 4th phase of NBRP, while continuing the existing activities, we aim to enrich genome-wide resources and high-demand timely resources to further improve the quality of our resources.

Key Strains/Studies

In fission yeasts, we can provide approximately 15,000 strains, including cell division- and sexual reproduction-related mutants, gene knock-out strains, GFP fusion gene expression strains, and conditional lethal mutant strains. We also can offer yeast strain sets according to the applications. In DNA resources, we can provide full-length cDNA clones (~1,600 clones), genomic DNA clones (~59,000 clones), genomic DNA and cDNA libraries, and various plasmid vectors (~1,400 clones).

For budding yeasts, approximately 14,000 strains are available, including mutant strains related to cell cycle, cell wall synthesis, autophagy, and meiosis specific DNA recombination; ribosome synthesis related strains; series of genome-wide chromosome partial duplicated strains; series of double knock-out strains of various sets of protein phosphatase genes; conditional mutant collection by auxin induction degron method; DNA barcode strain collection; and model budding yeast mutant strains other than *S. cerevisiae*. Additionally, we offer genome-wide single gene overexpression resource named gTOW6000 (~5,800 strains) and various plasmid vectors (~6,300 clones).

● Autophagy-related vectors (pRS316[GFP-ATG8], pRS416GAL1[ATG13], pRS416GAL1[ATG13-8SA], pRS315[mCherry-ATG8])

The kinase complex of Atg1 and Atg13 is essential for starvation-induced macroautophagy. Both kinases are regulated by phosphorylation, but the enzyme responsible for Atg13 dephosphorylation has not been identified. By analyzing Ptc2 and Ptc3, which are phosphatases involved in various pathways, we found that these enzymes act to promote macroautophagy by dephosphorylating Atg1 and Atg13 (Fig. 1. *PNAS* 116: 1613-1620, 2019).

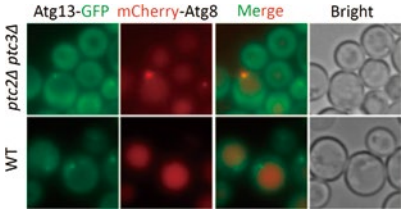


Fig. 1. Decreased pre-autophagosome structures (Atg13 protein aggregation: green spots) and vacuolar fusion of autophagosome (red) in the *ptc2/3* double mutant under rapamycin-induced autophagy (From *PNAS* 116: 1613-1620, 2019 Fig. 3b)

Prokaryotes (E. coli, B. subtilis)

Core Facility : Genetic Resource Center, National Institute of Genetics
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Contact site : genkaku@nig.ac.jp
E. coli URL : https://shigen.nig.ac.jp/ecoli/strain/
B. subtilis URL : https://shigen.nig.ac.jp/bsub/

Overview

Escherichia coli *Bacillus subtilis*

Escherichia coli, a prokaryote, is widely used as a research material. A great deal of biological knowledge and experimental methods related to genetics, biochemistry, and molecular biology is accumulated. Many basic genes common to the biogenic of eukaryotes, including humans, are also conserved in *E. coli*. Therefore, *E. coli* is expected to remain an extremely important resource as a model organism for all living organisms. Furthermore, *E. coli* has another important aspect as a production bacterium at industrial level. *Bacillus subtilis* is a gram positive soil bacterium. It is an important model organism of prokaryotic cells as it has biological characteristics different from *E. coli*, which is a gram-negative enteric bacterium. *B. subtilis* is also used for industrial production of various degradative enzymes.

In NBRP-Prokaryotes, the core facility, National Institute of Genetics collects, preserves, and provides *E. coli* and *B. subtilis* resources, phages, and antibodies developed in Japan. The sub-core facility, Kyushu University is in charge of backing up the resources. In the 4th phase of NBRP, information of actual mutation sites in strains and plasmid physical maps will be released to increase the added value of each resource, and information on genes, strains, and gene maps will be integrated to improve the convenience of the database.

Key Strains/Studies

The resources being distributed are all non-pathogenic strains, and *E. coli* and *B. subtilis* resources are derived from K12 strain and 168 strain, respectively. In *E. coli*, we provide mutant strains (~15,000 strains, including comprehensive gene deletion strains and transposon-disrupted strains) and gene clones (~19,000 clones with His tag or GFP). We also can provide cloning resources (~470 vectors and ~80 host strains), including host strain for iVEC ultra simple cloning (*J Bacteriol* 201: e00660-18 2019), as well as phages and antibodies. For *B. subtilis*, following resources can be provided: gene mutation/knock-out strains [~7,200 strains, including a collection of ~4000 genes of drug cassette substitution type DNA barcode strains (*Cell Syst* 4: 291-305.e7, 2017)], chromosomal deletion strains (~350 strains), and gene clones (~4,400 clones).

● *E. coli* Keio Collection

5-Fluoropyrimidines (e.g., 5-FU) are anticancer drugs effective for colon cancer; however, their efficacy varies among patients, and the mechanism of action of these drugs is unclear. To investigate the contribution of gut microbiota on drug efficacy, nematodes-*E. coli*-5-FU interactions were analyzed as a model system. The analysis revealed that 5-FU does not act directly on nematodes, but exerts its effect by acting on the metabolism of vitamin B6, B9, and ribonucleotides in *E. coli* (Fig. 1 *Cell* 169: 442–456.e18, 2017).

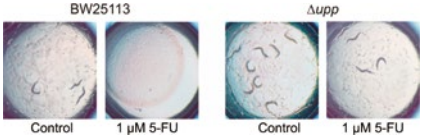

Fig. 1. Relevant genes and mechanisms in *E. coli* were screened through viability evaluation of nematodes treated with 5-FU in media containing normal strain (right: BW25113) and comprehensive gene-deleted strains of *E. coli* [left: (*Δupp*) for example] (From *Cell* 169: 442-456.e18, 2017 Fig. 2).

● Cell division- and rDNA-related mutants of *Bacillus subtilis*

The condensin complex, which is essential for nucleoid formation in *B. subtilis*, is induced in the *Spo0J-parS* region near the origin of DNA replication. However, these deletion mutants did not show any impairment in nucleoid separation. Alternatively, aberrant cells containing non-separated nucleoids are observed in mutants that have one copy of rDNA among the multiple ribosomal RNA loci (rDNAs) near the replication origin. Analysis of rDNA has revealed that condensin binds to rDNA and that at least two copies of rDNA are required for normal nucleoid separation (Fig. 2, *Cell Rep* 21: 1347-1360, 2017).

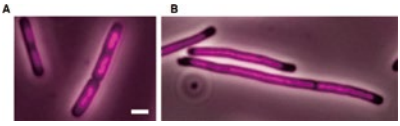

Fig. 2. *Spo0J* gene deletion strain (left) and double deletion strain of *spo0J* and rDNA (one copy only) (right) of *Bacillus subtilis*. In the double deletion strain, the nucleoid (reddish purple: DAPI staining) is elongated. (From *Cell Rep* 21: 1347-1360, 2017 Fig. 6A, B).

Core Facility : Microbe Division/Japan Collection of Microorganisms (JCM),
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Overview

Microorganisms are characterized by species diversity. In addition to our living environment, microorganisms inhabit various environments, including symbiosis with hosts and extreme environments in terms of temperature, pH, barometric pressure, salt concentration, humidity, and radiation. These diverse functions of microorganisms have been used in a wide range of research, including ecosystem maintenance, environmental remediation, and production of food and drugs.

In NBRP-General microbes, RIKEN BRC-JCM (Japan Collection of Microorganisms) collects, preserves, and provides diverse microbial strains. In quality control of these strains and the entire operation, we strive to ensure credibility by conducting under the international quality management standard ISO9001 certification. We help rescue microbial resources which are valuable but are facing a difficulty to be preserved at some laboratories. We also collaborate with NBRP-Pathogenic eukaryotic microbes and NBRP-Pathogenic bacteria to complement microbial resources required for research and development. In the 4th phase of NBRP, while enriching the information related to the strains such as physiological characters, genomes, and related publications in our catalogue database, we will strive to improve the convenience of the database for promoting microbial research in the world.

Top: Certified ISO9001
Photos, upper left: *Bifidobacterium longum subsp. longum* inhibiting infection of enteric pathogens.
Upper right: *Lactococcus lactis subsp. lactis* stimulating entire immune system (Gram-stained image).
Lower left: Avermectin-producing *Streptomyces avermitilis*, isolated by the Novel Prize laureate Prof. Ōmura.
Lower right: *Cryptococcus terricola* producing biodiesel from starch.

Key Strains/Studies

A total of approximately 19,600 strains of various non-pathogenic microbial strains belonging to bacteria (including lactic acid bacteria and actinomycetes), archaea, yeast, and filamentous fungi are released. We maintain a large number of type strains representing species equivalent to approximately half of internationally recognized bacteria, archaea, and yeast, and strains isolated in the fields of fermentation and biotechnology. We also provide anaerobic bacteria and extremophiles that are difficult to culture. A large number of microorganisms useful for health research such as for human and animal indigenous microbiota, and those useful in biotechnology fields such as for food, agriculture, drug discovery, bioenergy, substance production, and environmental remediation, are available. In addition, we have self-decoded the genome sequence information of approximately 500 strains of bacteria, archaea, and fungi. This information is available in our home page.

● *Aquificae* bacteria, including *Thermosulfidibacter takaii* (JCM 13301)

The reductive TCA cycle is one of the oldest carbon assimilation pathways required for the biosynthesis of organic compounds. In *thermosulfidibacter*, a thermophilic, hydrogen-oxidizing, sulfur-reducing bacteria isolated from the deep sea, no known carbon-fixing enzymes involved in reductive TCA cycle were found by whole genome sequence analysis. Using transcriptome, proteome, trace metabolome analyses and so on, it was found that the responding direction of the TCA cycle was flexibly changed depending on the available carbon source with same enzymes. These results suggest that life may have come to being as something which flexibly change metabolism depending on the abundance of available inorganic and organic carbon sources (*Science* 359: 559-563, 2018).

Apart from this report, many research results using NBRP resources have been reported, such as the discovery that peptides in natto have pneumococcus-specific antibacterial activity (Fig. 1, *AMB Express* 7: 127, 2017) and development of a single culture medium suitable for the culture of several human enteric bacteria (*Biosci Biochem Biotech* 81: 2009-2017, 2017; *Int J Biochem Cell Biol* 93: 52-61, 2017).

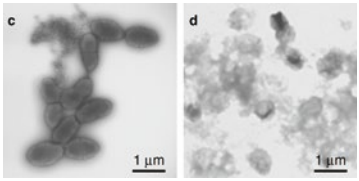


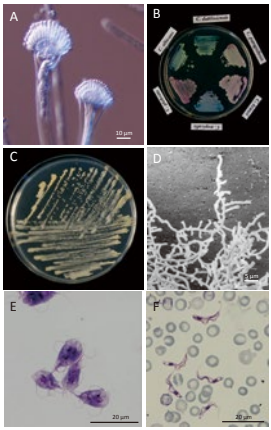
Fig. 1. Pneumococci are lysed in the presence of a natto-derived peptide (right). (From *AMB Express* 7: 127, 2017 Fig. 5c, d).

Core Facility : Medical Mycology Research Center, Chiba University
Principal Investigator : Takashi Yaguchi FAX : +81-43-226-2486
Contact site : bioresource@ml.chiba-u.jp (pathogenic fungi and actinomycetes; Chiba Univ.)
protozoa@tm.nagasaki-u.ac.jp (pathogenic protozoa; Nagasaki Univ.)
URL : https://pathogenic-microbes.nbrp.jp/

Overview

The need for infectious disease control is increasing nowadays. In addition to education and basic research on infectious diseases, research for new diagnostic reagents and drug development requires high-quality resources of pathogenic microorganisms.

In NBRP-Pathogenic eukaryotic microbes, the core facility, Medical Mycology Research Center of Chiba University, collects, preserves, and provides pathogenic fungi and actinomycetes. The sub-core facility, Nagasaki University Institute of Tropical Medicine collects, preserves, and provides pathogenic protozoa. We receive the deposit of clinical isolates through cooperation with medical institutions and support of clinical sites (e.g., identification of bacterial isolates, implementation of drug susceptibility tests, and cooperation on detection of pathogenic factors), and again provide them by adding molecular, morphological, physiological, and clinical information to users as reliable pathogenic strains. We aim to establish a collection that can reliably respond to any infections caused by pathogenic eukaryotic organisms in the future. This project also provides microorganisms in the form of DNA and inactivated forms to research institutions that are not able to handle pathogenic microorganisms as living cells. In the 4th phase of NBRP, while continuing the existing activities, we will focus on collecting clinically important species, and development of genomic information. By providing high value-added resources, we will contribute to basic and applied research in the field of medicine.



Fungi A) *Aspergillus fumigatus*, B) Various *Candida* (cultured at 25°C for 3 days). Middle row: *Actinomycetes*, C, D) *Nocardia farcinica*. Bottom row: Protozoa E) *Giardia intestinalis*, and F) *Trypanosoma brucei*.

Key Strains/Studies

We offer the following strains: fresh clinical isolates of fungi and actinomycetes, all species of highly pathogenic fungi (including Class III pathogens) and other major pathogenic fungal species (~15,000 strains), standard strains of pathogenic actinomycetes, mainly in the *Nocardia* genus (~2,700 strains), and human infectious protozoal strains (~350 strains).

● Azole-resistant *Aspergillus fumigatus* clinical isolate (IFM61567), *etc.*

Azoles are important therapeutic agents for aspergillosis due to *Aspergillus fumigatus* infection. However, situation is becoming serious as azole-resistant strains are spreading. As a result of screening for azole-resistance-related genes. *atrR* gene-deleted strains of azole-resistant *A. fumigatus* clinical isolates were highly susceptible to azoles (Fig. 1, *PLoS Pathog* 13: e100609, 2017).

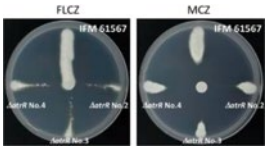


Fig. 1. Colony growth of the atrR gene-deficient strain (3 · 6 · 9 o'clock direction) is suppressed more than the resistant clinical strain (12 o'clock direction) when azoles (FLCZ and MCZ) are added to the center of the plate (From *PLoS Pathog* 13: e100609, 2017 Fig. 10A).

● *Plasmodium yoelii* 17XL strain (Py003) *etc.*

EBL family proteins are secreted from malaria parasites and bind to the molecules on the erythrocyte surface. A transgenic line of *Plasmodium yoelii* (a malaria parasite that infects rodents) in which the *ebl* gene expression was suppressed by the Tet-Off system, could not bind to erythrocytes and showed reduced invasion of erythrocytes and proliferation therein. (Fig. 2, *Parasitol Int* 67: 706-714, 2018).

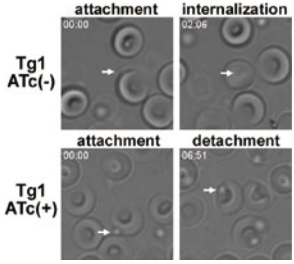


Fig. 2. *Plasmodium yoelii* binds to and invades an erythrocyte when EBL is expressed (upper), but binding to the erythrocyte is not maintained when expression is suppressed (lower) (From *Parasitol Int* 67: 706-714, 2018 Fig. 5a with modifications).

Pathogenic bacteria

Core Facility : Center for Conservation of Microbial Genetic Resource, Gifu University
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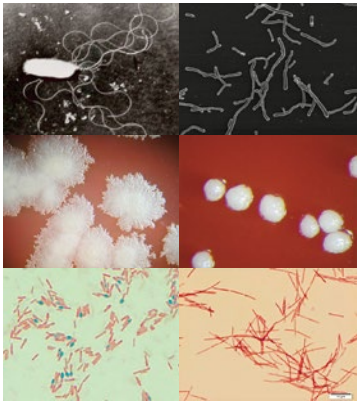
Overview

To counteract against emerging and re-emerging infectious diseases that are ongoing and are expected to continue, as well as rapidly progressing gene mutations and development of drug resistance, development of high-quality and excellent bioresources critical for these studies and a core institution that manages and provides these bioresources along with useful supplementary information is necessary.

Regarding NBRP-Pathogenic bacteria, the core facility, Gifu University collects, preserves, and provides bacteria causing infectious diseases and opportunistic infections in various fields. The sub-core facility, Osaka University collects, preserves, and provides bacteria responsible for enteric infections. In addition, the other sub-core facility, Gunma University is responsible for backing up these resources. The three organizations coordinate with each other to develop a more stable preservation system and to offer strains with useful information, including pathogenic factors, biochemical characteristics, drug susceptibility and resistance. In addition, we will conserve valuable bacteria resources deposited by researchers. To improve user convenience, we will create a database of preservation methods and culture methods for provided strains. We will work to support people involved in education, research, and development related to infectious diseases and pathogens.



A wide variety of pathogenic bacteria resources

Key Strains/Studies

Gifu University owns more than 20,000 bacterial strains including over 80% of strains pathogenic to human. We preserve phylogenetically related anaerobes and aerobic non-fermenting gram-negative bacteria. We also collect BSL2-3 specified pathogens, opportunistic pathogens, attenuated strains for educational purpose, and drug-resistant strains. The collection also includes variants within bacterial species, such as serotypes, which are important in the field of infectious diseases. Osaka University owns standard strains and clinical isolates mainly of pathogenic *E. coli*, *Vibrio bacteria*, and other enteropathogenic bacteria. A total of approximately 8,000 strains are publicly available on the NBRP Pathogenic Bacterial Database. As this project provides pathogenic microbes, we may ask ordering institutions to provide facility information or may place restrictions on database search, depending on bacterial species. If you are interested in such bacteria, please consult with our representative in advance.

● POR1: TDH (thermostable direct hemolysin)-negative strain derived from *Vibrio parahaemolyticus* clinical strain (RIMD2210633)

Vibrio parahaemolyticus is a major cause of food poisoning by fish and shellfish. T3SS2, which is a type III secretion system to inject effector proteins into host cells, is considered as the main virulence factor for gastroenteritis; however, the function of VopL, one of its effector proteins, in host infection was unknown. Analysis using the *vopL* gene deletion strains, which were prepared from POR1 strain, revealed that VopL inhibits the migration of the regulatory subunit of NADAPH oxidase (NOX) from the cytoplasm to the cell membrane and reduces reactive oxygen species production by destroying the normal cytoskeleton function by actin (Fig. 1, *PLoS Pathog* 13: e1006438, 2017).

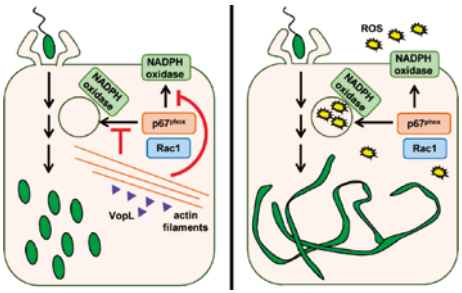


Fig. 1. Schematic diagram of suppression of reactive oxygen species production in host by VopL.
Left) Normal strain (green) suppresses NOX activity and proliferates. Right) In the *vopL*-deficient strain, reactive oxygen species (yellow) induce elongation of intracellular bacteria (suppression of cell division) and reduce proliferation. (From *PLoS Pathog* 13: e1006438, 2017 Fig. 8)

Human pathogenic viruses

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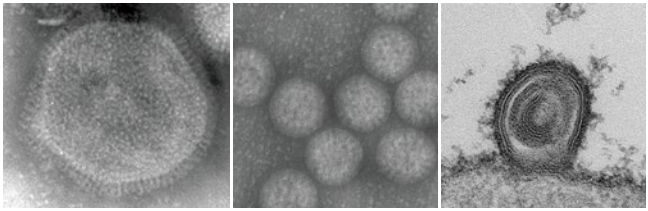
Overview

Currently, 168 families, 1,421 genera and 6,590 species of viruses have been registered to the International Committee on Taxonomy of Viruses. Among them, a few hundred species are human pathogenic. Furthermore, novel viruses have been identified as pathogens of emerging infectious diseases in the 21st century. Even in a virus species, there are many strains possessing different tropism, pathogenicity, antigenicity and other characteristics. To overcome viral diseases, the analyses of molecular mechanism of virus growth and disease progression and the developments of antivirals and vaccines using these viral strains are essential.

In NBRP-human pathogenic viruses, Nagasaki University, Hokkaido University, The University of Tokyo, Osaka University, and RIKEN are responsible for arboviruses and highly pathogenic viruses, zoonotic viruses including influenza viruses, herpesviruses, gastrointestinal viruses, and cDNA clones of virus genes, respectively. In addition, the database on the viruses which are stored in other universities and institutes in Japan will be also created to enhance effective use of virus resources.



(Left to right) Influenza A virus, Rotavirus, Herpes simplex virus type 1

Key Strains/Studies

The four universities, which are core facilities of NBRP-human pathogenic viruses, possess 28 species and 1,384 strains of viruses. We will further collect viruses from both within and outside Japan and also isolate viruses from clinical specimens. The database will be updated by the determinations of genome sequences of reference strains.

2021 is the first year of this NBRP. We will establish the system to collect, store and provide the virus resources within this year.

● Isolation of SARS-CoV-2 from clinical specimens and pathologic analysis using hamster

Many SARS-CoV-2 strains have been isolated from clinical specimens of COVID-19 patients. To establish an animal model to analyze COVID-19, the hamsters were intranasally inoculated with SARS-CoV-2. SARS-CoV-2 infection caused severe body weight loss, efficient virus growth in the lung and severe pneumonia in hamsters as well as in humans, suggesting that hamsters are highly susceptible to SARS-CoV-2 infection and appropriate animal models for COVID-19 analyses (Fig. 1).

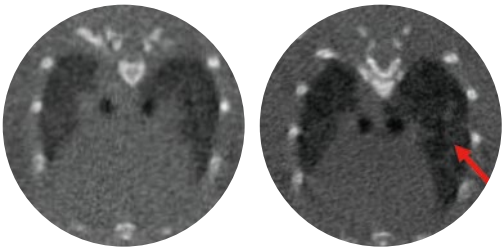


Fig. 1. CT images of the lung of the hamster infected with SARS-CoV-2
(Left) Pre-infection, (Right) 8 day post-infection, Red arrow: pneumonia.

Cord blood cells for research

Core Facility : Department of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science University of Tokyo (IMSUT)
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URL : https://cell.brc.riken.jp/en/

Overview

Human cord blood cells (CBCs) have been known as the source of hematopoietic stem cell transplantation for severe hematologic diseases like leukemia, and they are now widely used for research purposes in the medical and biological studies of regenerative medicine, drug development, epidemiology, infection, genetics and environmental studies.

This project provides frozen CBCs for research use, to researchers through the RIKEN BioResource Research center (BRC). The research CBs are collected with written consent in hospitals participating in this project, then transferred to the processing facility, The Institute of Medical Science, The University of Tokyo, Cell resource center (IMSUT CRC), where CBCs are processed, cryopreserved, and transferred to RIKEN BRC. Through the RIKEN BRC, research CBCs shall be provided to the researchers in need.

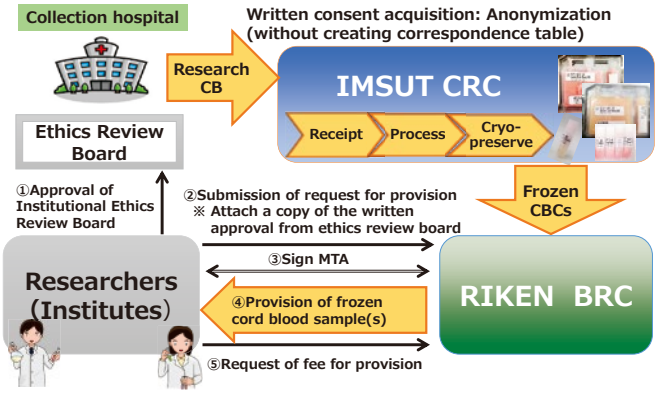


Fig. 1. Flow chart of collection, cell processing, cryopreservation, and provision of human CBCs for research, and method of application for use thereof

Key samples / Studies

All samples in this bank are frozen after processing. Nucleated cell samples contain whole white blood cells in cord blood. Mononuclear cell samples primarily consist of lymphocytes and monocytes, but also contain CD34-positive cells. CD34-positive cell samples carry representative markers of hematopoietic stem cells, attracting attention not only in hematopoietic stem cell transplantation research and blood differentiation research but also in regenerative medicine as a source of iPS cells. For frozen cord blood, infection test [HBs-Ag, HBc-Ab, HCV-Ab, HIV-I/II-Ab, HTLV-1-Ab, Syphilis (TPHA)] and sterility test are conducted.

● Examples of research results using this bank

Important issues such as recurrence and metastasis remain unsolved even with immunotherapy, which has recently been proven to be an effective treatment modality against cancer. Immunotherapy with NKT cells is expected to comprehensively activate innate and acquired immunity, it may be useful for treatment of any type of cancer. In fact, activated NKT therapy through NKT cell-specific antigen presentation by the glycolipid α-galactosylceramide (GC) (*via* GC-pulsed dendritic cells) has succeeded in substantially extending the survival of cancer patients in clinical research. Furthermore, among the GC derivatives, a synthetic glycolipid called RK that induces more potent antitumor effects has been developed. In an *in vitro* system using NKT cells differentiated from cord blood cell-derived iPS cells (NKT-iPS cells), RK-pulsed dendritic cells show significant improvements in multiple antitumor-related indices of NKT cells compared with GC-pulsed dendritic cells. In addition, long-term antitumor effects were also observed in mice (Fig. 2, *Front Immunol* 8: 1206, 2017).

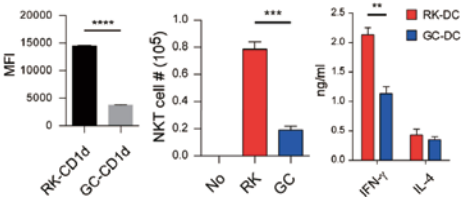


Fig. 2. Comparison of NTK cell activity indices between RK and GC
Left: Mean fluorescence intensity (MFI) of CD1d (dendritic cell surface antigen), Middle: Vα24+CD3+NKT cell count, Right: INF-γ and IL-4 concentrations in culture medium (From *Front Immunol* 8: 1206, 2017 Fig. 2 with partial modifications)

Human and animal cells

Core Facility : Cell Engineering Division, RIKEN BioResource Research Center
Principal Investigator : Yukio Nakamura FAX : +81-29-836-9130
Contact site : cellqa.brc@riken.jp (Regarding materials and methods)
cellbank.brc@riken.jp (Regarding deposit or provision)
URL : https://cell.brc.riken.jp/en/

Overview

Advances in genetic engineering techniques such as gene cloning by PCR technology and development of mutant mice by combining ES cells and homologous recombination technology have dramatically driven progress in functional analysis of genes in the late 20th century. In addition, reprogramming of cells by nuclear transfer technology and ES cell culture technology have led to revolutionary iPS cell technology in the 21st century. After "era of freely manipulating genes," "era of freely manipulating cells" has arrived. Consequently, the types of cell materials are also drastically increasing.

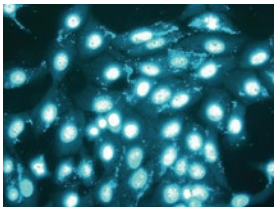


Fig. 1. DNA staining of cells. Not only nuclei but also cytoplasm are stained due to mycoplasma infection.

RIKEN BRC Cell Engineering Division is focusing on accepting deposition, preserving, and distributing high-quality and diverse cell materials. Increased use of cell materials can lead to frequent cell line mix-ups and mycoplasma contamination (Fig. 1), and results from experiments with such materials can be inaccurate and non-reproducible. In our division, we have developed a highly reliable system that provides cell specimens which are confirmed to be free of these problems. We are also working to incorporate cutting-edge technologies such as animal species identification using DNA sequencing. To reduce human error in quality control, we have introduced a quality control system under ISO9001 certification (Fig. 2). In addition, we are working to enrich additional information, including characteristics and culture methods of various cell lines such as cancer cells and human disease-specific iPS cells.

Fig. 2. Accreditation by ISO9001

Key Strains/Studies

We can provide following cells: Human cell lines including cancer cells and general cell lines derived from various animal species (~2,600 lines); cell lines for gene analysis consisting of healthy Japanese-derived immortalized cell lines, Sonoda-Tajima collection cells (mainly from various races and ethnic groups in South America), and Goto collection cells [derived from Werner syndrome patients] (~400 lines); and stem cell lines (~5,400 lines) including human somatic stem cells (human cord blood and mesenchymal stem cells), ES cells (human, marmoset, rabbit, and mouse), and disease-specific iPS cells and healthy human iPS cells (~3,600 and 480 lines, respectively) and animal iPS cells.

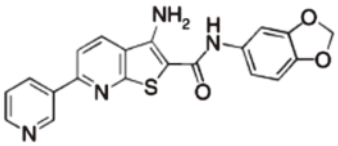


Fig.3. A drug candidate for amyotrophic lateral sclerosis (ALS)
One of the causal genes of ALS, mutated SOD1, interacts with an endoplasmic reticulum-resident membrane protein Derlin-1, and triggers motoneuron death. This chemical can inhibit interaction between mutated SOD1 and Derlin-1. (From *Nature Commun* 9: 2668, 2018 Fig.1g)

● Mouse osteoclast precursor-like cell RAW264 (RCB0535) and osteoblast-like cell ST2 (RCB0224)

RANK and its ligand RANKL mediate osteoclast maturation via osteocytes. Experiments with RAW264 and ST2 cells have demonstrated that they also act to promote bone formation by osteoblasts via osteoclasts and play a central role in linking bone resorption and bone formation. Furthermore, an antibody designed to bind to the RANKL extracellular domain and promote osteoblast activation was found to suppress bone resorption simultaneously with promoting bone formation in osteoporosis model mice (*Nature* 561: 195-200, 2018).

● iPS cells derived from patients with amyotrophic lateral sclerosis (ALS) (HPS0251, HPS0252, HPS0292)

SOD1 mutation is one of the causes of ALS. The SOD1 mutant binds to the endoplasmic reticulum DERL1 protein and eventually causes motor neuron death. Derivatives of SOD1-DERL1 binding inhibitors, which were discovered from screening by the TR-FRET method, inhibited death of ALS motor neurons induced from ALS patient-derived iPS cells carrying SOD1 gene mutations. Furthermore, when these derivatives were administered to transgenic mice with the mutant SOD1 gene, delayed onset and prolonged survival were also observed (Fig. 3, *Nat Commun* 9: 2668, 2018).

DNA material

Core Facility : Gene Engineering Division, RIKEN BioResource Research Center
Principal Investigator : Yoshihiro Miwa FAX : +81-29-836-9120
Contact site : dnabank.brc@riken.jp
URL : https://dna.brc.riken.jp/en/

Overview

Genetic material such as genomic and cDNA clones of human, animal and microbe origin, and genetic research tools such as genome editing vectors, fluorescent/ luminescent protein genes and viral vectors are one of the most important and fundamental bioresources for the life science. Genetic materials and tools are now widely utilized in numerous life science research fields not only in basic researches such as analyses of gene function and control mechanisms of gene expression but also in applied researches such as development of various therapies and drugs as well as material production.

RIKEN BioResource Research Center (BRC) Gene Engineering Division has been engaging in the collection, preservation, quality control and distribution of cutting-edge genetic materials and tools developed mainly by Japanese researchers. To provide scientific community with genetic materials and tools of the highest quality with assured reproducibility of experimental results, we perform rigorous quality control by testing growth, restriction enzyme mapping and nucleotide sequencing of clones. The Material Transfer Agreement is used for each transfer of genetic materials and tools to protect the intellectual property rights of developers and to define the responsibility of users. We have also opened a path of the academic use of advanced genetic materials and tools such as genome editing vectors and fluorescent/luminescent protein genes owned by commercial entities. Relevant information such as characteristics of bioresources and methodologies are provided via the web of the RIKEN BRC. For the best use of genetic resources, technical seminars and training courses are also given.

Genetic tools such as fluorescent protein (upper left) and comprehensive clones such as human cDNA and mouse BAC clones are collected and preserved. After quality test, we distribute them to researchers worldwide.

Key Genetic Materials and Tools

Comprehensive libraries such as cDNA clones corresponding to allmost all human genes, EST clones of mouse, common marmoset, clawed frog and ascidians, BAC clones covering almost entire genome of mouse, rat, Japanese macaque and Drosophila, and ORF clones of fission yeast and thermophile *T. thermophilus*. The clones can be searched in our web site and KEGG (Kyoto Encyclopedia of Genes and Genomes) database. By the collaboration within our center, we provide genomic DNA of microorganisms and mouse strains. Furthermore, we provide cutting-edge genetic tools such as near-infrared luciferase Akaluc, Fucci expression vectors for monitoring cell cycle progression in living cells, organelle markers, knock-in vectors for the regulation technology of protein degradation by the auxin degron method, expression vectors, plasmid clones for genome editing and gene transduction.

● Mitophagy visualization fluorescent sensor, mito-SRAI (cat# RDB18223)

Mitophagy is a selective autophagy degrading stress-damaged mitochondria. Dr. Miyawaki Atsushi and Dr. Katayama Hiroyuki of RIKEN Center for Brain Science (CBS) and Dr. Hioki Hiroyuki of Juntendo University and their colleagues have recently developed mito-SRAI, a fluorescent sensor that can quantitatively visualize mitophagy both in live and fixed conditions. The mito-SRAI is composed of TOLLES (cyan) fluorescent protein that is resistant to acidic condition and protein degradation in lysosomes, and YPet (yellow) fluorescent protein whose fluorescence intensity changes according to pH. The mito-SRAI is specifically localized in mitochondria and has been genetically engineered to confer tolerance of fluorescence in fixed conditions.

The mito-SRAI might support drug discovery assays testing a huge amount of fixed biological samples and experimental animal studies. The mitophagy can be observed by representative ratio (TOLLES/ YPet) images by expressing in cultured cells (Fig 1., Katayama, H. *et al*., *Cell* 181 (5): 1176-1187, 2020. PMID: 32437660).

URL:https://dna.brc.riken.jp/en/gsb0000en/gsb0021en

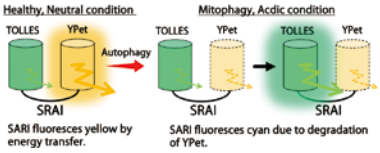


Fig.1. mito-SRAI visualizes mitophagy in not only living cells but also fixed biological samples.

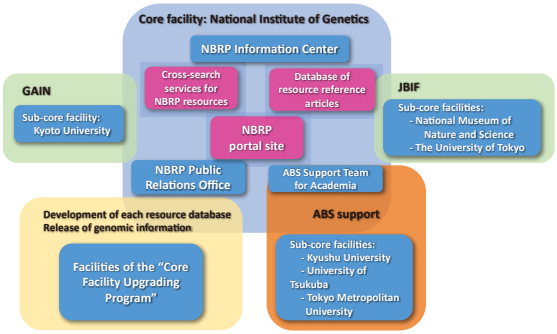
Core Facility : Genetic Resources Center, National Institute of Genetics
Principal Investigator : Shoko Kawamoto FAX : +81-55-981-6886
Contact site : nbrp@shigen.info
URL : https://nbrp.jp/

Overview

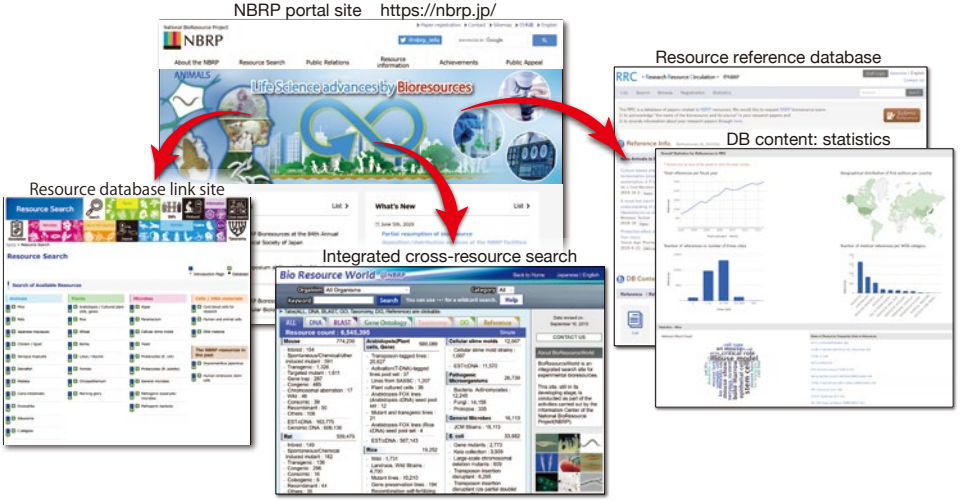
The Information Center Upgrade Program promotes the following five efforts by seven organizations: (1) NBRP Information Center activities, (2) the Great Ape Information Network (GAIN) activities, (3) the Japan Node of the Global Biodiversity Information Facility (GBIF) activities, (4) Access and Benefit Sharing (ABS) support, and (5) public relations activities for NBRP.

The primary task of NBRP Information Center is the development of bio-resource databases (1). The Information Center is established at the National Institute of Genetics (NIG) and supports the development of bio-resource information databases for each species of the Core Facility Upgrading Program. Resource users can search approximately 6.5 million NBRP resource data and around 40,000 scientific articles that have used or cited these resources by the information center cross-search service. The Center also supports the release of genomic information sequenced by the Genomic Information Upgrading Program. The Information Center also works together with GAIN (2) and JBIF (Japan Initiative for Biodiversity Information) (3) to support their information dissemination through their respective websites. In addition, the ABS Support Team for Academia and the NBRP Public Relations Office have been established in NIG. ABS Support Team for Academia works as a general contact office for ABS-related matters in cooperation with the sub-core facilities (4). NBRP Public Relations Office works closely with all organizations participating in the NBRP programs and manages the NBRP portal site and engages in various outreach activities to promote the dissemination and use of bio-resources (5).

The organization of the Information Center Upgrading Program



NBRP portal site https://nbrp.jp/



INFORMATION CENTER UPGRADING PROGRAM Information (GAIN)

Sub-Core Facility : Wildlife Research Center, Kyoto University
Principal Investigator : Genichi Idani FAX : +81-568-62-2428
Contact site : gain@pri.kyoto-u.ac.jp
URL : https://shigen.nig.ac.jp/gain/

Overview

The Gain website https://shigen.nig.ac.jp/gain/

Research using great apes is extremely important for understanding human nature. The *Hominidae* family is currently classified into four genera (*Hominidae Homo*, *Hominidae Pan*, *Hominidae Gorilla*, and *Hominidae Pongo*) in terms of biology and law. To understand human beings, it is essential to understand the other three genera in the *Hominidae* family. Alternatively, they are endangered species. The so-called Washington Convention prohibits international commercial trading of these species. Therefore, chimpanzees, gorillas, and orangutans in Japan are extremely valuable in terms of species conservation and academic research.

The Great Ape Information Network (GAIN) project collects and manages information, such as the history, family, genome, behavior, and other materials about all individuals of valuable endangered species such as great apes in Japan, including individuals in zoos. By providing them for joint use by researchers all over the country, we promote the development of academic research and conduct activities to promote the welfare and conservation of great apes.

INFORMATION CENTER UPGRADING PROGRAM Information (GBIF)

①Sub-Core Facility : Center for Colletions, National Museum of Nature and Science
Principal Investigator : Utsugi Jinbo
②Sub-Core Facility : Graduate School of Arts and Sciences, The University of Tokyo
Principal Investigator : Shigeto Dobata
Contact site : http:// www.gbif.jp/v2/en/contact/
URL : http:// www.gbif.jp/v2/en/

Overview

The JBIF website http:// www.gbif.jp/v2/en/

Ecosystems on the earth are constructed by various organisms that interact with each other. As a species on earth, humans benefit from biodiversity in many ways, from food, clothing, and shelter to economic activities. To maintain biodiversity for the future, it is necessary to understand the mechanisms and preserve the biodiversity.

To share biodiversity information in the world and create a mechanism that anyone can freely access, the Global Biodiversity Information Facility (GBIF) conducts the following activities: (1) development of biodiversity information infrastructure to be used for research and policy decision purposes, (2) accumulation and provision of biodiversity information, (3) development of information accumulation and analysis tools, and (4) support of activities and development of skills related to biodiversity information. Japan Initiative for Biodiversity Information (JBIF, formerly GBIF Japan Node) promotes the use of biodiversity data in Japan and disseminates its presence to the world. The National Museum of Nature and Science provides biodiversity information utilizing the network of natural history museums. The University of Tokyo is in charge of collecting domestic and foreign information and standardizing biodiversity information.

Core Facility : Genetic Resources Center, National Institute of Genetics
General contact office : ABS Support Team for Academia, NIG INNOVATION Mutsuaki Suzuki
①Sub-Core Facility : Material Management Center, Kyushu University
Principal Investigator : Katsuya Fukami
②Sub-Core Facility : Makino Herbarium, Tokyo Metropolitan University
Principal Investigator : Noriaki Murakami
③Sub-Core Facility : Tsukuba Plant Innovation Research Center, University of Tsukuba
Principal Investigator : Kazuo Watanabe
Contact site : abs@nig.ac.jp, msuzuki@nig.ac.jp
TEL : +81-55-981-5831 FAX : +81-55-981-5832
URL : http://www.idenshigen.jp/

Overview

●Nagoya Protocol Implementation (compliance with laws and regulations on access and utilization of genetic resources from overseas)

To access overseas plants, animals and microorganisms, it is inevitable to observe relevant national laws of provider countries. The Nagoya Protocol on Access and Benefit-Sharing (ABS) was brought into effect in 2014 to effectively share benefits among countries that provide genetic resources and those that use genetic resources. On August 20, 2017, Japan became the 99th party of the Nagoya Protocol, and domestic measures (ABS guidelines) were launched on the same day. Relevant laws and regulations of each country are on the way to be developed, and contracts with providers (mutual agreed terms: MAT) and permission from the provider country government (prior informed consent: PIC) are required to use the genetic resources of those countries. However, there might be some cases in which individual researchers may not be able to solve because the scope, enforcement, and development status of laws and regulations related to ABS differ from country to country, and ABS procedure is still unclear.

●Implementation system of support and enlightenment

In Japan, with the three cooperative institutions of Kyushu University, University of Tsukuba, and Tokyo Metropolitan University, National Institute of Genetics is developing a system to support the procedures of the permit (PIC) and the contract with the provider (MAT) as part of the NBRP Information Center Upgrading Program. The three institutions are in charge of the following tasks: The Material Management Center, Kyushu University is in charge of supporting the acquisition of genetic resources in the field of biotechnology and the development of tools such as contract templates; Tsukuba Plant Innovation Research Center, University of Tsukuba is in charge of supporting genetic resource acquisition, considering the role of genetic resources in the field of breeding and horticulture and the related seed banks; Makino Herbarium, Tokyo Metropolitan University is in charge of supporting the acquisition and use of genetic resources in the field of biodiversity research based on studies of ABS-related case studies in Asia.

The ABS Support Team for Academia, NIG INNOVATION at the National Institute of Genetics supports universities and research institutes for acquiring genetic resources from overseas as a general contact office for ABS-related matters in Japan. In addition, we have established a website to post ABS information database, comprehensive search site, and related materials. We also conduct visiting free seminars and provide email and phone consultations (please use the contact information above). Furthermore, as a university system construction WG, we are examining the university system construction with partner schools consisting of Tokyo University of Marine Science and Technology, Mie University, Nagasaki University, Nagoya University and others.

Website for the ABS Support Team for Academia

●International activities related to overseas genetic resources

We participate in and discuss at international conferences such as the Conference of the Parties (to cope with issues such as digital sequence information).

Core Facility : Japanese Association for Laboratory Animal Science
Principal Investigator : Chihiro Koshimoto FAX : +81-3-3814-3990
Contact site : jinzaiikusei@jalas.jp
URL : http://www.m-kenshou.org/

Overview

There is no doubt that the results of medical and life science research have contributed greatly to the stability of people's lives. Animal experimentations also play an important role in this. On the other hand, it is also essential for animal experimentations to be conducted appropriately based on social consensus without failing to take animal welfare into consideration. For this reason, the “Basic Guidelines for the Conduct of Animal Experiments, etc.” established by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) etc. requires research institutions to ensure social transparency through external verification of animal experiments. Since 2016, the NBRB has been implementing a program to strengthen and promote the external verification system for animal experiments, and has worked to significantly reinforce the verification system and increase the rate of external verification implementation.

In the second phase of the project, “Fostering and Utilizing Human Resources to Promote External Validation,” which started in 2021, we will continue to make efforts to ensure the appropriateness of animal experiments conducted in Japan. In this project, we will support the implementation system of external validation by continuing to maintain the number of validation specialists trained in the first phase of the project, improve and standardize their quality. We will also strive to raise awareness by holding steady and continuous briefing sessions for research institutions that plan to undergo external validation.

In the second phase of the project, we will expand the scope of education and awareness to include parties involved in animal experiments in Japan. By doing so, we aim to improve the understanding of a wide range of people, including clerks and technicians at institutions involved in animal experiments, and to focus our efforts on the optimization of the animal experiment implementation system. The improvement of the environment for conducting animal experiments, including the appropriate use of animal resources for research, is an important point that will support the future of Japan, which claims to be a science-oriented country. By spreading the education widely and meticulously to the personnel involved in animal experiments and sharing the correct information, we believe that it is very significant to create an environment where appropriate animal experiments can be conducted at each site that supports the institutional management system, thereby fostering social understanding and trust. In order to communicate the appropriateness of the institutional management system of animal experimentations to the public and to deepen common understanding, we will play a role in supporting and enhancing the external validation system through this project.

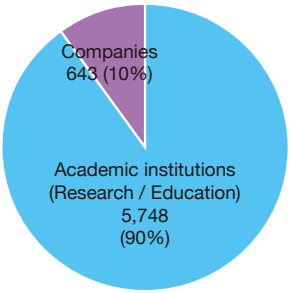
Human Resources Development Workshop for External Verification (left) and a briefing session on external verification (right)

Outcomes of NBRP Activities

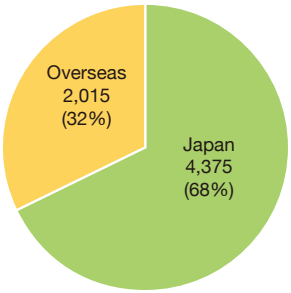
In the past five years (FY2016–FY2020), the average number of depositors of bioresources was **468** per year, and the average number of users was **6,390** per year. Many individuals related to research, education, and business have used NBRP.

The current activities and their results are shown below.

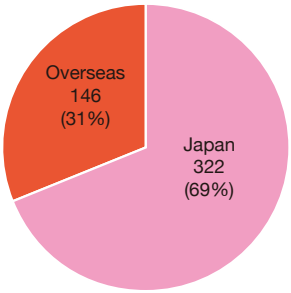
● Percentage of average annual users by organization type (past 5 years)



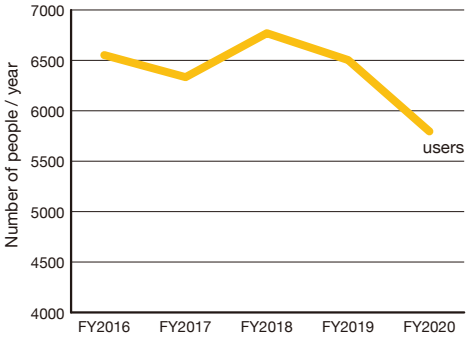
● Percentage of average annual users in Japan and overseas (past 5 years)



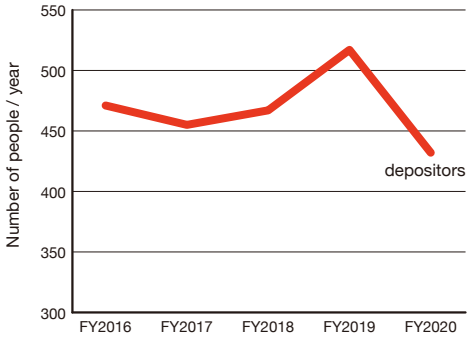
● Percentage of average annual depositors in Japan and overseas (past 5 years)



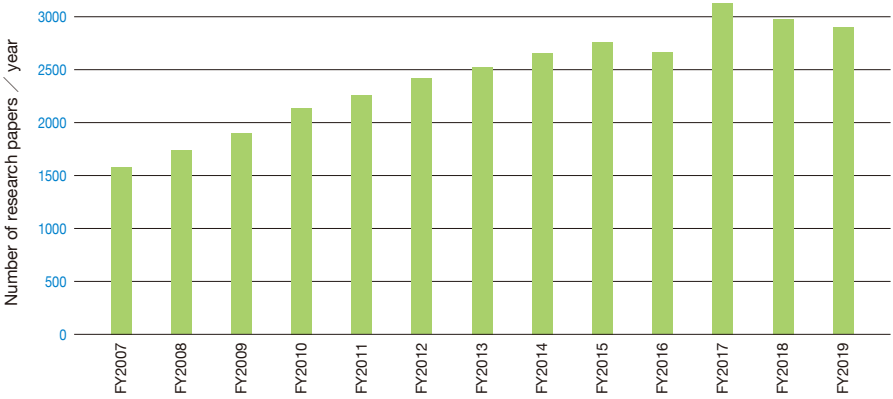
● Trends in the number of users (past 5 years)



● Trends in the number of depositors (past 5 years)

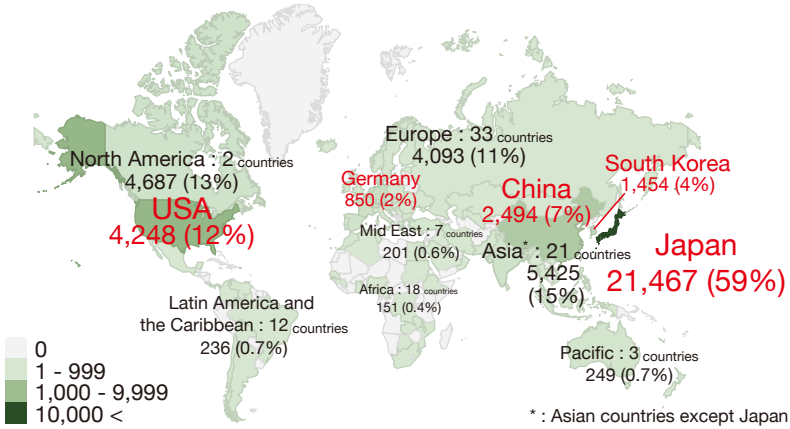


● Trends in the number of research papers published using NBRP resources



Number of NBRP related publications are shown up until 2019, since there is a time lag between bioresource provision and publication.

● Global distribution of authors (first authors) of papers on research outcomes using NBRP resources (as of May 2021)



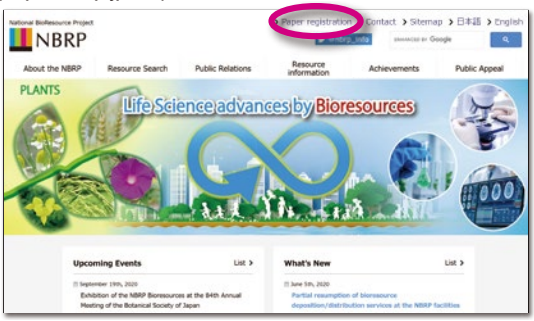
Feedback of Research Outcomes Using NBRP Resources

● Collection of Research Paper Information

Accumulation of research outcome using bioresources can further enhance the value of the bioresources. NBRP is collecting such research outcomes, and integrating them into the NBRP database. Therefore, we would like to request the bioresource users 1) to describe "the name of the bioresource and its supplier" in the research papers and 2) to send the paper information to the NBRP Core Facility, upon publication of research outcome using the NBRP resources.

Please visit to the research paper registration site for easy feedback of such information.

Please click "Paper registration", on the NBRP portal (https://nbrp.jp/en/)



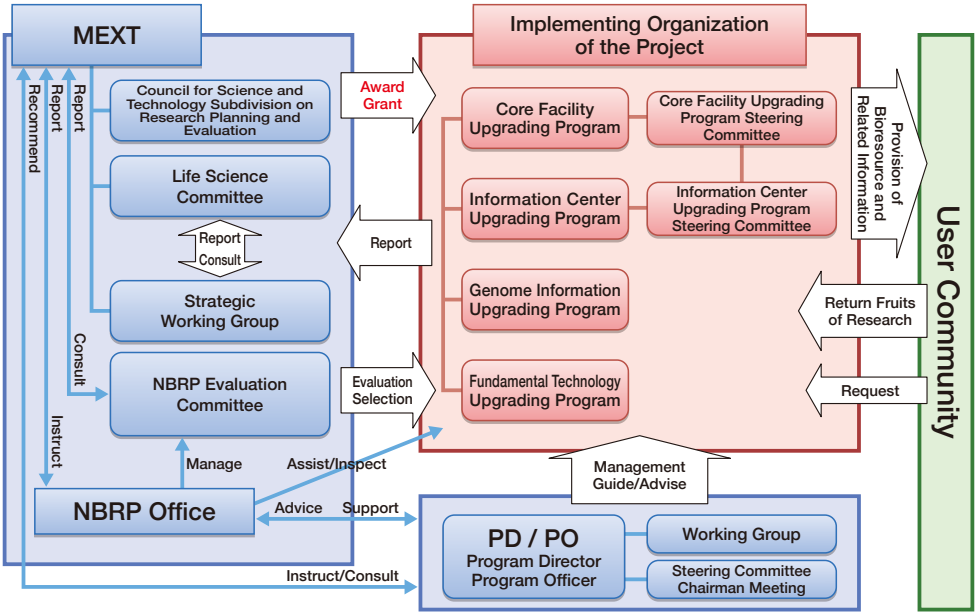
● Deposit of Bioresources

It is important for the development of life science research in Japan to make the newly developed and collected bioresources continuously available to research communities. In this project, these resources will be deposited with the appropriate institutes for implementation of the "Core Facility Upgrading Program" (see p1–p31). These institutions will do the work of reproducing, sending, and documenting the resources needed to provide research communities on your behalf.

Depositors can add various conditions for using the deposited resources, such as citation of published articles, restrictions on purpose of use, and requirement of separate license agreement for commercial use.

For consultation on deposit, please contact an appropriate institute for implementation of the "Core Facility Upgrading Program".

Project Implementation System



NBRP Program Director (PD)

NBRP-PD coordinates the operation of the project and the cooperation and promotion of each program.

Name	Affiliated organization
Yuji Kohara	Director, Database Center for Life Science, Research Organization of Information and Systems

NBRP Program Officer (PO)

NBRP-PO assists the PD and promotes the operation of each task.

Name	Affiliated organization
Yuichi Obata	Special Advisor, RIKEN BioResource Research Center (BRC)
Satoshi Tabata	Vice President / Director, Kazusa DNA Research Institute
Tetsuya Hayashi	Professor, Graduate School of Medical Sciences, Kyushu University

Changes in bioresources developed by NBRP and the core facilities

	Bioresource / Subject (Core Facility)	1st Phase FY2002~2006	2nd Phase FY2007~2011	3rd Phase FY2012~2016	4th Phase FY2017~2021
Animal	Mice (RIKEN BRC)	✓	✓	✓	✓
	Mice: ENU Mutagenesis (RIKEN GSC)	✓			
	Rats (Kyoto University)	✓	✓	✓	✓
	Japanese macaques (National Institute for physiological Sciences)	✓	✓	✓	
	Japanese macaques (Kyoto University)				✓
	Chicken / Quail (Nagoya University)			✓	✓
	Xenopus tropicalis (Hiroshima University)	✓	✓	✓	✓
	Zebrafish (RIKEN CBS : Former name is RIKEN BSI - FY2017)	✓	✓	✓	✓
	Medaka (Nagoya University)	✓			
	Medaka (National Institute for Basic Biology)		✓	✓	✓
	Ciona intestinalis / Oxycomanthus japonicus (University of Tsukuba)		✓		
	Ciona intestinalis (University of Tsukuba)			✓	✓
	Drosophila (Kyoto Institute of Technology)	✓	✓		
	Drosophila (National Institute of Genetics)			✓	✓
	Silkworms (Kyushu University)	✓	✓	✓	✓
	C. elegans (Tokyo Women's Medical University School of Medicine)	✓	✓	✓	✓
Plant	Arabidopsis / Cultured plant cells, genes (RIKEN BRC)	✓	✓	✓	✓
	Rice (National Institute of Genetics)	✓	✓	✓	✓
	Wheat (Kyoto University)	✓	✓	✓	✓
	Barley (Okayama University)	✓	✓	✓	✓
	Lotus / Glycine (University of Miyazaki)	✓	✓	✓	✓
	Tomato (University of Tsukuba)		✓	✓	✓
	Chrysanthemum (Hiroshima University)	✓	✓	✓	✓
	Morning glory (Kyushu University)	✓	✓	✓	✓
Microbes	Algae (National Institute for Environmental Studies)	✓	✓	✓	✓
	Paramecium (Yamaguchi University)			✓	✓
	Cellular slime molds (University of Tsukuba)		✓	✓	
	Cellular slime molds (RIKEN BDR : Former name is RIKEN QBiC - FY2017)				✓
	Yeast (Osaka City University)	✓	✓	✓	✓
	E.coli (National Institute of Genetics)	✓			
	Prokaryotes (E.coli, B.subtilis) (National Institute of Genetics)		✓	✓	✓
	General microbes (RIKEN BRC)		✓	✓	✓
	Pathogenic microorganisms (Chiba University)	✓	✓	✓	
	Pathogenic eukaryotic microbes (Chiba University)				✓
	Pathogenic bacteria (Gifu University)				✓
	Human pathogenic viruses (Nagasaki University)				✓ FY2020~
Cell / DNA material	Cord blood stem cells for research (Tokai Univ. FY2012, 13→The Univ. of Tokyo FY2014 -)			✓	
	Cord blood cells for research (The University of Tokyo)				✓
	Human ES cells (Kyoto University)	✓	✓		
	Human and animal cells (RIKEN BRC)	✓	✓	✓	✓
	DNA (Animals and microorganisms) (RIKEN BRC)	✓			
	DNA material (RIKEN BRC)		✓	✓	✓
Total Number of Bioresources (Animals, Plants, Microbes)		**24**	**27**	**29**	**31**
Information	Information center (National Institute of Genetics)	✓	✓	✓	✓
	GAIN (Kyoto University)*	✓	✓	✓	✓
	GBIF (National Museum of Nature and Science / The Univ. of Tokyo)*		✓	✓	✓
	ABS support (NIG / Kyushu Univ. / Tokyo Metropolitan Univ. / Univ. of Tsukuba)*			✓ FY2015~	✓
	Human resource development for external verification (JALAS)			✓ FY2016~	✓

* : Sub-Core Facilities in the Information Center Upgrading Program

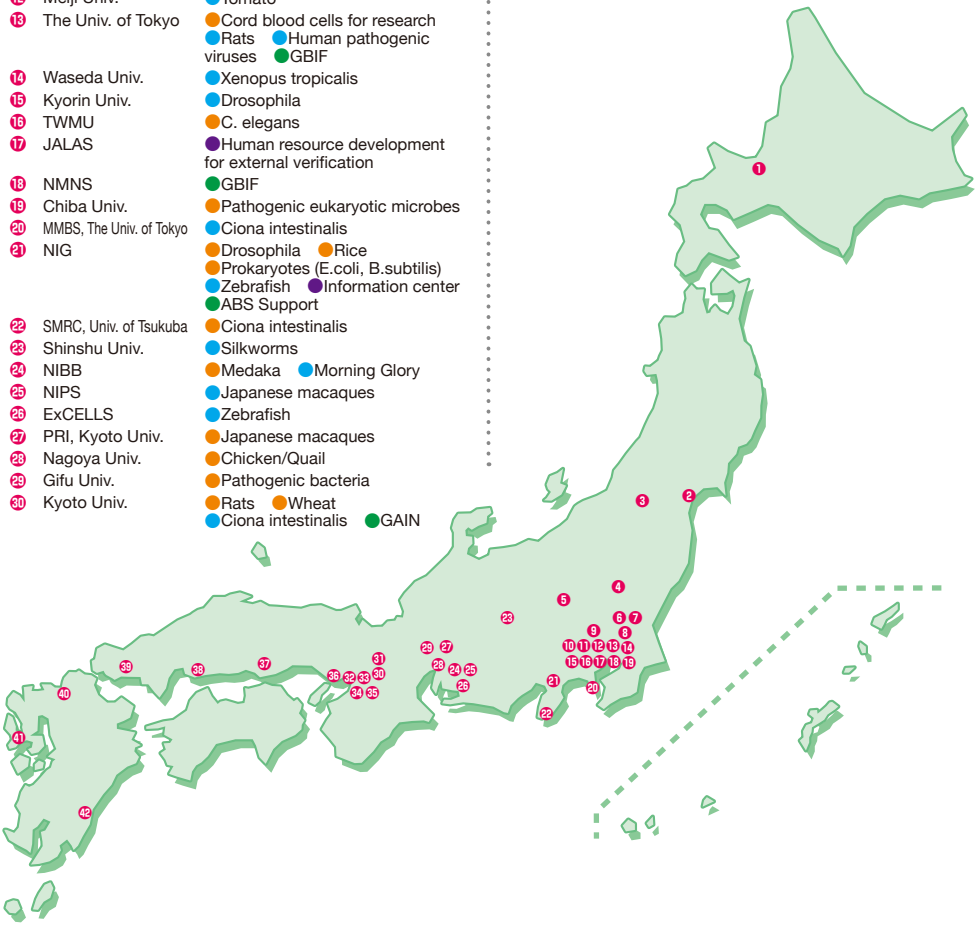
History of NBRP

1996	July	The First Science and Technology Basic Plan was decided at the Cabinet.
2001	January	RIKEN BioResource Center was established in Tsukuba.
2002	April	National BioResource Project (NBRP) was started and led by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, as a part of Research Revolution 2002 (RR2002).
	April	Beginning of the first phase of NBRP (22 resources). The project was composed of the Core Facility Upgrading Program and the Information Center Upgrading Program.
2003	April	Two resources were added to the Core Facility Upgrading Program.
	December	The NBRP exhibition was held at the 26th Annual Meeting of the Molecular Biology Society of Japan (continued every year). The exhibition was also held in the meetings of other academic societies.
2006	June	Publication of "Report for the Bioresources Upgrading Strategy", prepared by the Working Group on Bioresources Upgrading Strategy of the Life Science Committee.
2007	April	Beginning of the second phase of NBRP (27 resources).
	April	The Genome Information Upgrading Program and the Fundamental Technology Upgrading Program were added to NBRP.
	December	MEXT and the NBRP Promotion Committee visited the implementation organizations of the NBRP with the aim of engaging in discussions with principal investigators and directors of the organizations ("Site Visit").
2008	March	The second phase NBRP Kick-off Symposium, titled "Bioresources that Open the Future of Life Sciences", was held.
2009	April	NBRP, which was a MEXT project, began to be operated under the Grant for Promotion of Shared Use of R&D Facilities.
	August	Submission of the "Report on Database Upgrading and Dissemination of Outcome Information at NBRP" and the "Report on Desired Forms of Provision Fee and Protection of Intellectual Properties at NBRP" by the working group.
2010	February	Notification of "Basic Principles for Handling and Shipping Costs at NBRP".
	October	The 2nd International Meeting of Asian Network of Research Resource Centers was held in Tsukuba.
2011	June	Publication of "Report on Future Vision on Bioresources Upgrading" by the Life Science Committee.
	August	Following the Great East Japan Earthquake, the "Symposium on Disaster Mitigation on Bioresources" was held.
2012	January	The 10th anniversary open symposium to report the achievements of NBRP was held.
	April	Beginning of the third phase of NBRP (29 resources).
	November	The symposium "Challenges in the Third phase of NBRP" was held.
2013	October	The 5th International Meeting of Asian Network of Research Resource Centers was held in Hayama.
	December	Publication of "A Report on Desired Implementation of the Nagoya Protocol" (Ministry of the Environment).
2015	January	The open symposium to present about the achievements of NBRP (at the middle of the third phase) was held.
	April	The Operation of NBRP was transferred from MEXT to the Japan Agency for Medical Research and Development (AMED).
2016	May	The report "Desired Future Bioresource Upgrading" was prepared by the Life Science Committee.
	October	The 8th International Meeting of Asian Network of Research Resource Centers was held in Kyoto.
2017	April	Beginning of the fourth phase of NBRP (30 resources).
	December	The fourth phase NBRP Kick-off Symposium, titled "Research outcomes in basic and applied research using NBRP bioresources", was held.
2019	December	The NBRP Open Symposium at the middle of the fourth phase, was held.
2020	June	NBRP has constructed labor-saving and remote monitoring (remote sensing) system in bioresource maintenance to preserved its stable activity even in the face of crises such as COVID-19.
2021	March	The number of resources increases to 31 with the addition of the Human pathogenic viruses (NBRP fourth phase).
	April	NBRP is operated again by MEXT.

NBRP Network of Japan

Core Facility Upgrading Program : ●Core facilities ●Sub-core facilities
Information Center Upgrading Program : ●Core facilities ●Sub-core facilities

1. Hokkaido Univ. — ●Algae ●Human pathogenic viruses
2. Tohoku Univ. — ●Lotus/Glycine
3. Yamagata Univ. — ●Xenopus tropicalis
4. Utsunomiya Univ. — ●Medaka
5. Gunma Univ. — ●Pathogenic bacteria
6. Univ. of Tsukuba — ●Tomato ●Cellular slime molds ●ABS Support
7. NIES — ●Algae
8. RIKEN BRC — ●Mice ●Arabidopsis/Cultured plant cells, genes ●General microbes ●Human and animal cells ●DNA material ●Rats ●Human pathogenic viruses ●Cord blood cells for research
9. RIKEN CBS — ●Zebrafish
10. Tokyo Metropolitan Univ. — ●ABS Support
11. Gakushuin Univ. — ●Silkworms
12. Meiji Univ. — ●Tomato
13. The Univ. of Tokyo — ●Cord blood cells for research ●Rats ●Human pathogenic viruses ●GBIF
14. Waseda Univ. — ●Xenopus tropicalis
15. Kyorin Univ. — ●Drosophila
16. TWMU — ●C. elegans
17. JALAS — ●Human resource development for external verification
18. NMNS — ●GBIF
19. Chiba Univ. — ●Pathogenic eukaryotic microbes
20. MMBS, The Univ. of Tokyo — ●Ciona intestinalis
21. NIG — ●Drosophila ●Rice ●Prokaryotes (E.coli, B.subtilis) ●Zebrafish ●Information center ●ABS Support
22. SMRC, Univ. of Tsukuba — ●Ciona intestinalis
23. Shinshu Univ. — ●Silkworms
24. NIBB — ●Medaka ●Morning Glory
25. NIPS — ●Japanese macaques
26. ExCELLS — ●Zebrafish
27. PRI, Kyoto Univ. — ●Japanese macaques
28. Nagoya Univ. — ●Chicken/Quail
29. Gifu Univ. — ●Pathogenic bacteria
30. Kyoto Univ. — ●Rats ●Wheat ●Ciona intestinalis ●GAIN
31. Kyoto Insti. of Technology — ●Drosophila
32. Osaka City Univ. — ●Yeast
33. Osaka Univ. — ●Yeast ●Pathogenic bacteria ●Human pathogenic viruses
34. Osaka Prefecture Univ. — ●Tomato
35. RIKEN BDR — ●Cellular slime molds
36. Kobe Univ. — ●Algea
37. Okayama Univ. — ●Barley
38. Hiroshima Univ. — ●Xenopus tropicalis ●Chrysanthemum ●Yeast
39. Yamaguchi Univ. — ●Paramecium
40. Kyushu Univ. — ●Silkworms ●Morning Glory ●Prokaryotes (E.coli, B.subtilis) ●Rice ●ABS Support
41. Nagasaki Univ. — ●Pathogenic eukaryotic microbes ●Human pathogenic viruses
42. Univ. of Miyazaki — ●Lotus/Glycine ●Medaka



NBRP

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