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—Review—
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The Mouse Resources at the RIKEN BioResource Center

Atsushi YOSHIKI, Fumio IKE, Kazuyuki MEKADA, Yasuyuki KITAURA, Hatsumi NAKATA, Noriko HIRAIWA, Keiji MOCHIDA, Maiko IJUIN, Masayo KADOTA, Ayumi MURAKAMI, Atsuo OGURA, Kuniya ABE, Kazuo MORIWAKI, and Yuichi OBATA

RIKEN BioResource Center, 3–1–1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan

Abstract: Mice are one of the most important model organisms for studying biological phenomena and diseases processes in life sciences. The biomedical research community has succeeded in launching large scale strategic knockout mouse projects around the world. RIKEN BRC, a comprehensive government funded biological resource center was established in 2001. RIKEN BRC has been acting as the core facility for the mouse resources of the National BioResource Project (NBRP) of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan since 2002. RIKEN BRC is a founding member of the Federation of International Mouse Resources (FIMRe) together with the Jackson Laboratory, the European Mouse Mutant Archive, and other centers, and has participated in the International Mouse Strain Resource (IMSR) to distribute mouse strains worldwide. With the support of the scientific community, RIKEN BRC has collected over 3,800 strains including inbred, transgenic, knockout, wild-derived, and ENU-induced mutant strains. Excellent mouse models for human diseases and gene functions from academic organizations and private companies are distributed through RIKEN BRC. To meet research and social needs, our mice will be rederived to a specific pathogen-free state, strictly monitored for their health, and accurately tested for their genetic modifications and backgrounds. Users can easily access our mouse resources through the internet and obtain the mouse strains for a minimal fee. Cryopreservation of embryos and sperm is used for efficient preservation of the increasing number of mouse resources. RIKEN BRC collaborates with FIMRe members to support Japanese scientists in the use of valuable mouse resources from around the world.
Key words: genetic background, genetic manipulation, genome, inbred strain, quality control

The Mouse Resources with Advanced Technologies and Knowledge

The mouse is a small-sized mammal with adult weights ranging from 10 to 40 grams. They are easy to handle and grow to reproductive maturity at around 8 weeks of age. Females are easily bred under laboratory conditions with a mean litter size of 5–10. Males in most cases do not harm their young, so breeding pairs can be maintained in the same cage. Mice can proliferate and gener-

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Address corresponding: A. Yoshiki, Experimental Animal Division, RIKEN BioResource Center, 3–1–1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan

ate a maximum of four generations in a year.

The mouse has been widely used as an experimental animal in the biomedical research for over one hundred years [33]. Recent molecular studies demonstrated that common laboratory mice were originated from crossbred mice of different subspecies of *Mus musculus* ranging over distinct geographical locations [46, 58]. To date, a number of genetically uniform inbred strains with different characteristics have been established for biomedical research [5]. These enable us to precisely reproduce animal experiments with the same genetic materials. The inbred strains have brought revolutionary advancement, especially to cancer and immunology research [33].

At the beginning of the 21st century, the entire mouse genome was decoded [57], following the human genome [54], and its information has become public via the internet. Comparative studies of the mouse and the human genome have revealed that approximately 99% of mouse genes correspond to human counterparts. Moreover, comprehensive cDNA libraries have been created for mice and are available worldwide [44]. Transgenic and gene-targeting technologies have enabled us to manipulate the mouse genome and test a specific gene function *in vivo* [6, 10, 11, 14]. The mouse is the only mammal in which an *in vivo* gene function can be directly tested by genetic manipulations through embryonic stem (ES) cells.

Cryopreservation of embryos and sperm is widely used for mice and secures long-term storage of the increasing resources [12, 34]. New reproductive engineering techniques have been invented and applied to mouse genetics [42]. The development of pluripotential stem cell lines such as germline stem (GS) and induced pluripotential stem (iPS) cells together with ES cells, has further extended the use of mouse resources in regenerative biology and medicine [22, 50]. The mouse has played a leading role in the development of our understanding of epigenetic changes such as methylation and imprinting of the gene, which can be inherited without changes in DNA sequences [28].

With these advanced technologies and accumulated knowledge, the mouse is one of the most important model organisms for studying biological phenomena and pathogenesis of complex diseases in life sciences. In this context, the biomedical research community has successfully persuaded their government agencies in the US, Canada, and European countries to launch large-scale strategic mutagenesis projects for mice to target every gene, in order to establish research resources for unraveling human gene functions [3, 4, 8].

Establishment of RIKEN BioRsource Center

The RIKEN BioRsource Center (BRC) was established in 2001 as a global not-for-profit public institution financed by the Japanese Government providing biological materials, technical services, and educational programs to academic organizations and private enterprises around the world. RIKEN BRC is the only specialized comprehensive biological resource center in Japan, and operates under three principles; trust, sustainability, and leadership. RIKEN BRC aims to promote life sciences and the bio-industry with bioresources of the highest quality, to build up bioresources that are the essential infrastructure for sustainable development of mankind, and to develop new cutting edge bioresources.

Since 2002, RIKEN BRC has been designated as the core facility for mouse resources by the National BioResource Project (NBRP) of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

RIKEN BRC is a founding member of the Federation of International Mouse Resources (FIMRe). FIMRe is a collaborating alliance of mouse repositories worldwide, including the Jackson Laboratory, European Mouse Mutant Archive (EMMA), and the Center for Animal Resources and Development (CARD), Kumamoto University [9, 15]. We have participated in the International Mouse Strain Resource (IMSR), a one-stop web shop of mouse strains available from FIMRe member organizations. The RIKEN BRC is also a founding member of the Asian Mouse Mutagenesis and Resource Association (AMMRA), the purpose of which is to promote mouse mutagenesis projects and to facilitate access to mouse resources in Asia.

Mouse Strains Available from RIKEN BRC

With support from the scientific community, RIKEN BRC has collected over 3,800 mouse strains including

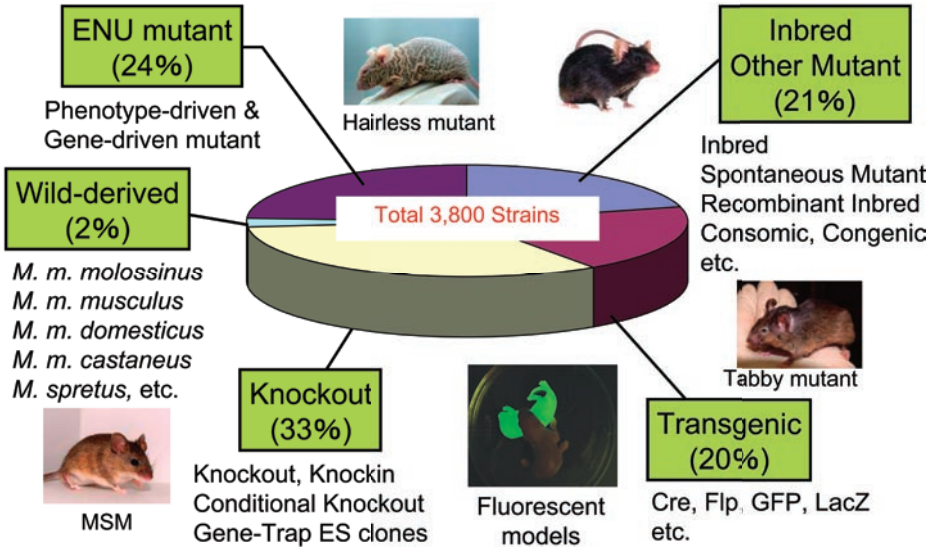

Fig. 1. Collection of the mouse resources at RIKEN BRC. The mouse strains are classified into five groups. The numbers in parentheses indicate the proportions (%) of each group.

inbred, spontaneous mutant, recombinant inbred, consomic, transgenic, knockout, wild-derived, and ENU-induced mutant strains (Fig. 1). These strains are useful models for studying gene functions and disease processes in various fields. The latest information on the mouse strains can be obtained from the RIKEN BRC web site. The excellent models that have the highest demand are briefly described below with the BRC registered number (RBRC) of the strain. Genomic DNA, organs, and tissues of each strain can also be provided on request.

Tools for visualizing biological events in vivo

Two transgenic strains of *fluorescent*, *ubiquitination-based cell cycle indicator*, "Fucci", B6.Cg-Tg(Fucci)596Bsi (RBRC02707) and B6.Cg-Tg(Fucci)504Bsi (RBRC02706) mice can be used to clearly visualize the cell-cycle with fluorescent markers, i.e. G1 phase nuclei red and those in S/G2/M phases green *in vivo*. The double transgenic mice in which every cell nucleus exhibits either red or green fluorescence will serve as a powerful tool for visualizing the spatio-temporal dynamics of cell-cycle progression in every biological event [37, 40, 48].

The Nanog-GFP transgenic mouse strain (RBRC02290) is useful for generation of iPS cells. Since the *Nanog* gene is a good candidate marker for pluripotency, pluripotential stem cells established from this strain can easily be monitored by the expression of the green fluorescent protein (GFP) [45].

The GFP-LC3#53 (RBRC00806) is the first transgenic model which can be used to visualize autophagy by the expression of a fusion gene encoding GFP and LC3. Autophagy is considered to play a key role in maintaining homeostasis in eukaryotes. When GFP-LC3#53 transgenic mice are subjected to stress or pathological conditions, autophagy can be detected through cytoplasmic fluorescent signals [27, 29, 56].

The C57BL/6-Tg(CAG-EGFP)C14-Y01-FM131Osb mice (RBRC00267), so-called "Green mice" have been widely used in various fields including cell biology, developmental biology, and cell/tissue transplantation experiments [18, 35, 43].

Knockout mice

The PD-1 deficient mouse is a model for autoimmune dilated cardiomyopathy [39]. The programmed cell death 1 (*Pdcd1*, *PD-1*) gene encodes an immune-inhibitory receptor that belongs to the CD28 family, and plays a role in the suppression of proliferation, differentiation, and class switching of B cells. Homozygous *Pdcd1*^{tm1Hon}-deficient mice of BALB/c background (RBRC00903, 00904) exhibited severe autoimmune dilated cardiomyo-

pathy, while those of C57BL/6 background (RBRC02142) show less severe symptoms.

The *Trp53*^{tm1Sia} mutant allele was created by homologous recombination using TT2 ES cells originated from an F_1 embryo of C57BL/6NCrj and CBA/JNCrj mice [53]. Homozygous mutant mice can grow after birth, but often suffer from the development of tumors in various regions of the body. Congenic strains have been developed with backgrounds of C57BL/6N (RBRC01361), C3H/HeN (RBRC00107), ICR (RBRC01348), DBA/2NCrj (RBRC01518), and MSM (RBRC00815).

The *p27* knockout mouse (B6;129P2-*Cdkn1b*^{tm1Kin}, RBRC01878) is useful for cell cycle research and tumor biology [36]. p27 (cyclin-dependent kinase inhibitor 1B) is one of the inhibitors of a series of cyclin and cyclin-dependent kinase (CDK) complex which plays a central role in the regulation of cell cycle progression. Homozygous *p27*-deficient mice display a variety of abnormalities such as increased body size with enlarged organs. About half of the mutants develop tumors originating from the intermediate lobe of the pituitary gland.

Conditional knockout mice

The floxed *RBP-J* mice (B.Cg-*Rbpj*^{tm1Hon}, RBRC01071) have a loxP-flanked *Rbpj* allele [17]. Rbpj, recombination signal binding protein for immunoglobulin kappa J region, which is a transcriptional factor of a Notch/RBP-J signaling pathway, plays a role in fate determination in various lineages. Conditional *Rbpj*-deficient mice can be generated by crossing site-specific Cre-transgenic mice.

The floxed *p38alpha* mice (B6.129-*Mapk14*$^{tm1.2Otsu}$, RBRC02192) have a loxP-flanked *p38alpha* allele. *p38alpha*, one of the p38 mitogen-activated protein (MAP) kinase subfamily, is widely expressed and has an important function in cytokine production and in the response to many types of stress. Because homozygous *p38alpha*-deficient mice (RBRC00361) are embryonically lethal at midgestation [51], floxed *p38alpha* mice are useful for investigating the roles of p38 MAP kinase pathway in adult tissues [38].

Cre and Flp-recombinase transgenic mice

A transgenic mouse that expresses a recombinase in a site-specific manner is essential for a conditional knockout mouse carrying a floxed allele. Cre from the bacteriophage P1 and Flp from *Saccharomyces cerevisiae* are both well-established recombinases for this purpose [16, 47]. While the conditional knockout resources are expanding due to recent international efforts, there is an increasing demand for the establishment of an archive of high quality tissue-specific Cre-drivers, so-called Cre-zoo. We have already collected useful Cre- and Flp-transgenic mice (Table 1) and distributed them internationally. The following strains are frequently requested.

Table 1. Cre and Flp-transgenic mouse strains

Recombinase	Tissue-specificity	Number of strains
Cre	Brain and nervous system	40
Cre	Embryogenesis	11
Cre	Germ cells	14
Cre	Immune cells	2
Cre	Skeletal Muscle	1
Cre	Ubiquitous	1
FLP	CAG, EF1-alpha	4
	Total	73

The B6.Cg-Tg(CAG-cre)CZ-MO2Osb mice (RBRC01828) express the Cre recombinase gene throughout the body under the control of a CAG promoter. The Emx1-Cre strain (RBRC00808) was created by a knockin strategy, inserting a cre recombinase gene into the *Emx1* gene. The specific expression of Cre recombinase was observed in the dorsal telencephalon, neocortex, hippocampus, and olfactory bulb [21]. B6-Tg(CAG-FLPe)36 mice (RBRC01834) are useful for more complex dual approaches that combine FLP and Cre [23].

Wild-derived strains

Since laboratory inbred strains have been genetically refined through intensive inbreeding, they have accumulated mutations on their genomes, lost a number of original traits and allelic variants [26]. Therefore, the wild-derived strains must serve as an important resource to find novel allelic variations and modifier genes [59]. The wild-derived mouse strains at the RIKEN BRC, including 42 strains, 4 species of *Mus* and 5 subspecies

of *Mus musculus*, are unique and the world's largest mouse resource of genetic diversity.

MSM (RBRC00209) is a wild-derived inbred strain originated from Japanese wild mice, *Mus musculus molossinus* [32]. MSM mice have several unique phenotypes, such as small size (<15 g), low incidence of tumor development, and distinct behaviors, making them promising resources for higher brain functions and lifestyle-related diseases by expanding genome diversity. MSM mice are especially invaluable in the search for novel functions of the genome due to the availability of the MSM genomic BAC libraries, their end sequence information, ES cells and consomic strains with a C57BL/6 background [1, 2, 49].

ENU-induced mutant mice

ENU-induced mutant mice carry mutations, namely point mutations, randomly induced by the *N*-ethyl-*N*-nitrosourea (ENU). Interesting models for human diseases have been recovered by the phenotype- and gene-driven approaches [13].

The *Gdf5*^{Rgsc451} strain (RBRC-GSC0080) is a model for osteoarthritis (OA). OA is the most common form of joint disorder, and is characterized by the degeneration of articular cartilage. A new *Gdf5* allele, *Gdf5*^{Rgsc451}, carries an amino acid substitution (W408R) which is a dominant negative form of GDF5 protein. The heterozygous mutant mice exhibit brachypodism and ankylosis, while the homozygous mice suffer from much severer phenotypes associated with early-onset of OA [30].

DISC1 has been reported as a causative gene of human depression and schizophrenia. Two independent mutations in exon 2 of the *Disc1* gene were successfully recovered from the archive of G1 genomic DNA and frozen sperm by the gene-driven approach. The *Disc1*^{Rgsc1390} (RBRC02324) and *Disc1*^{Rgsc1393} (RBRC02325) strains have been developed and established as models for depression and schizophrenia, respectively [7].

Other useful mouse resource

Gene-trap mouse ES cell clones [20] for the production of knockout mice were deposited at the Cell Engineering Division of RIKEN BRC. Recently, mouse ES cells derived from standard inbred strains have also become available from the Cell Engineering Division. The inbred ES cell lines derived from C57BL/6N and C57BL/6J should be especially valuable for gene-targeting to establish a knockout mouse of their pure genetic backgrounds [52].

Mouse Strains with Licensed Technology or Products

RIKEN BRC has executed a license agreement with TET Systems Holding (Heidelberg, Germany) to receive, maintain, reproduce, use, and distribute transgenic mice using the Tet Technology [25]. Amalgaam (MBL) (Tokyo, Japan) also signed and agreed to the deposition of Fucci mice, which can be used to visualize the "cell cycle" *in vivo* [40, 48]. These biotech companies have allowed RIKEN BRC with generous terms and conditions to distribute the mouse strains containing their excellent technologies or products to not-for-profit academic researchers. Thus, the NBRP core facility of the mouse resource has been recognized as a reliable dissemination partner by these private entities.

How to Use the Mouse Resources

Users can access our mouse strains through the websites of RIKEN BRC and IMSR (Fig. 2). Users must complete a Material Transfer Agreement (MTA) for Distribution and an order form. Some strains require permission of use from the Depositor using an approval form. In addition, animal experiments in Japan must be conducted with special attention to animal welfare, safety, environmental conservation, and research ethics. Therefore, all recipients of mouse resources must submit their experiment plans and protocols to their organization's Animal and Recombinant DNA Experiments Committees to obtain authorized approvals. RIKEN BRC starts to prepare the mice upon receipt of the order documents from the users. We provide mouse resources for a minimal fee solely to reimburse the RIKEN BRC for a part of the preparation and handling costs of the requested mouse resources. This reimbursement fee is indispensable to continuing our activities of distribution. Recipients will also bear the shipping cost. The recipient of the mouse resource must expressly describe that "the mouse strain was provided by the RIKEN BRC

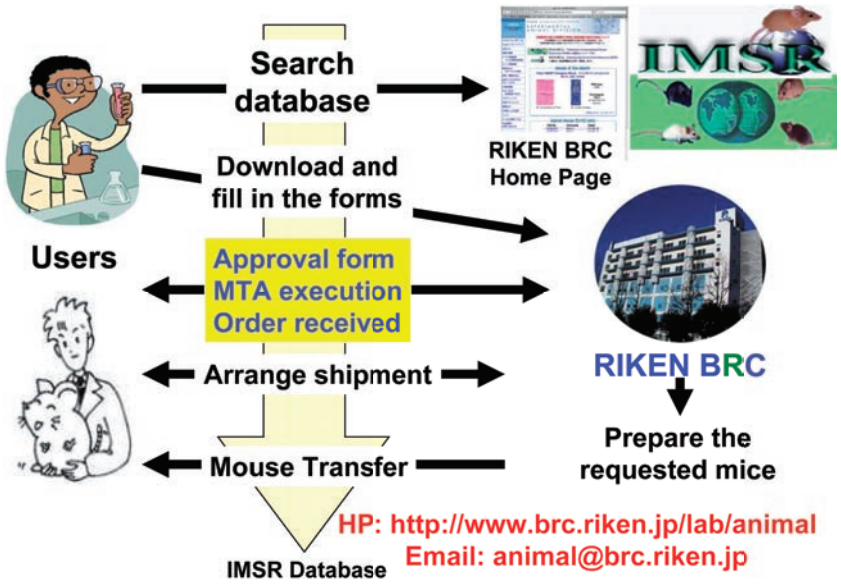

Fig. 2. Schematic flow of how to use our mouse strains. Users can easily access to our mouse strains through the internet.

through the National BioResource Project of the MEXT, Japan", in the Materials and Methods section of its publication.

Husbandry in the Barrier Facility

The animal rooms are kept at 24 ± 2°C with relative humidity of 55 ± 5%, and supplied with HEPA-filtered fresh air under a light cycle of 12L/12D (08:00 on, 20:00 off). The air pressure in each area is regulated to maintain a clean environment within the barrier facility. Sensitive strains are supplemented with commercial paper nests (Regular Shack, Shepherd Specialty Papers, Tennessee, USA). The mice are freely given gamma-irradiated food (CE2, CLEA Japan, Inc., Tokyo) and filtered drinking water. All supplies including caging with paper bedding and drinking water in the bottles are sterilized by autoclaving. Humans must take a wet shower and wear sterilized clothing, eyes-only-hoods, rubber shoes, disposable masks, and gloves prior to entry into the barrier. A card key system safeguards the barrier facility and helps to minimize microbial contamination carried by humans.

Mice are kept in an individually-ventilated microisolation cage system. Cage exchange is conducted at one or two-week intervals by qualified animal technicians. The mice are handled with disinfected forceps covered with silicon rubber caps or gloved hands. The mice are identified by ear punch. Their breeding records are kept on cage cards and digital files in a Filemaker database.

Health and Genetic Quality

All the mouse strains deposited at RIKEN BRC are subjected to rederivation treatments by embryo transfer or hysterectomy prior to entering the barrier facility. Jcl:ICR and BALB/cA-*nu*/+ females (CLEA Japan, Inc., Tokyo) are used as recipients for embryo transfer and foster mothers, respectively. Various disease models and wild-derived strains have successfully been rederived using BALB/cA-*nu*/+ foster mothers.

Health monitoring of mouse strains is one of the most important quality control programs. Periodic monitoring for major pathogens is done in every rack of the facility using sentinel mice exposed to dirty bedding [19]. Pathogens monitored are classified into four classes and listed in Table 2. Immunocompetent BALB/cA-*nu*/+ females are used as sentinel mice, because they are free from all pathogens listed in Table 2. Sentinel mice are tested for the class A and B pathogens. The sentinel mice

Table 2. Classification of pathogens in health monitoring at RIKEN BRC

Classification	Pathogens
A	*C. piliforme*, Ectromelia virus, Lymphocytic choriomeningitis virus (LCMV), Mouse hepatitis virus (MHV), *M. pulmonis*, Sendai virus (HVJ)
B	*C. rodentium*, *C. kutscheri*, Dermatophytes, *P. pneumotropica*, Salmonella spp., *H. hepaticus*, *H. bilis*, Ectoparasites, Intestinal protozoa, Pinworms
C	*S. aureus*, *P. aeruginosa*, *P. carinii*
D	Pneumonia virus of mice (PVM), Mouse encephalomielitis virus (TMEV/GDVII), Minute virus of mouse (MVM), Reovirus type 3 (Reo3), Mouse adenovirus (MAV), Mouse rotavirus (EDIM), Mouse cytomegalovirus (MCMV), Lactate dehydrogenase elevating virus (LDHEV)

kept in the rack for immuno-deficient strains are monitored for the class C pathogens as well. The class D list contains pathogens rarely detected in the Japanese facilities hence mice are sent to the ICLAS monitoring center of the Central Institute for Laboratory Animals, Kawasaki, Japan for class D examination whenever requested. The test results are published regularly as a HEALTH CERTIFICATE on our website. The environment of the facility is monitored quarterly for bacteria and fungi in every room and area.

Genetic monitoring is another integral part of our quality control programs. Genetically-modified strains such as transgenic and knockout mice are genotyped by using PCR with allele-specific primers. The genotyping PCR protocols have been optimized and made public on our website. Genetic backgrounds of congenic strains are monitored with simple sequence length polymorphism (SSLP) markers [55]. Inbred and wild-derived strains are also monitored with standard biochemical markers [41]. Recently, single nucleotide polymorphisms (SNPs) analyses were conducted among inbred and wild-derived strains to clarify any subtle or comprehensive genetic differences [31]. Thus, RIKEN BRC distributes microbiologically and genetically high-quality mouse strains to investigators.

Cryopreservation

In order to cope with increasing resources, cryopreservation is a key technology for efficient and economic management of the mouse resource facilities. The mouse strains in high-demand and of low-survivor after freeze-thawing are the only ones kept as live animals. Most strains are cryopreserved as embryos or sperm whenever possible. The embryos are produced by *in vitro* fertilization and vitrified at the 2-cell stage in EFS (ethylene glycol, ficoll, and sucrose) solution [24] in 1.8 ml plastic tubes. Mutant and genetically engineered strains are frozen as sperm in 18% raffinose and 3% skim milk solution [34] in plastic straws. The frozen embryos and sperm are stored in DR-430LM liquid nitrogen tanks (Taiyo Nippon Sanso Corporation, Tokyo, Japan). A backup storage facility was established in 2007 at the Harima Institute, 500 km away from Tsukuba, to minimize the risk from disasters.

International Recovery of Frozen Strains

Most of the strains are cryopreserved as embryos, gametes and ES cells in the FIMRe organizations. Many biomedical researchers, however, do not have their own technical expertise or facilities to rederive live mice from frozen stock and they have difficulties in using the frozen strains for their research. To improve this situation, RIKEN BRC recently executed agreements with other FIMRe members for international recovery of mouse strains from distant repositories to facilitate the use of frozen strains (Fig. 3). Japanese scientists are encouraged to use frozen strains from distant repositories of the FIMRe by this support system through RIKEN BRC.

Finally, RIKEN BRC continues to make efforts for the establishment of mouse resources that meet the highest global standard by advanced quality control tech-

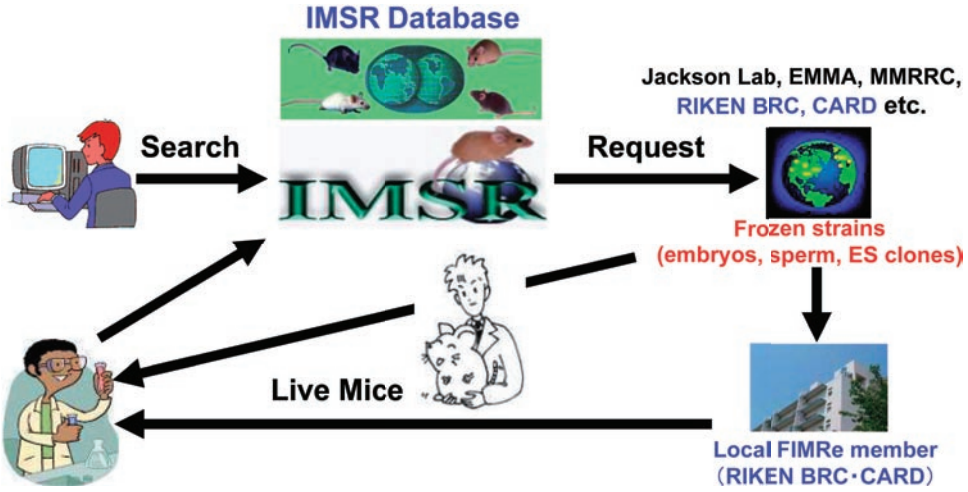

Fig. 3. International recovery of frozen strains. A scientist can search for an interesting strain in the IMSR. A local FIMRe member provides technical assistance for recovery of live mice from frozen strains.

nologies and standardized phenotypic information for functional genomics.

Acknowledgment(s)

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Relevant URLs

RIKEN BRC http://www.brc.riken.jp/
NBRP http://www.nbrp.jp/
MEXT http://www.mext.go.jp/
FIMRe http://www.fimre.org/
The Jackson Laboratory
http://www.jax.org/
CARD, Kumamoto University
http://card.medic.kumamoto-u.ac.jp/
EMMA http://www.emmanet.org/
AMMRA http://www.ammra.info/
Experimental Animal Division, RIKEN BRC
http://www.brc.riken.jp/lab/animal/
Cell Engineering Division, RIKEN BRC
http://www.brc.riken.jp/lab/cell/
TET Systems Holding
http://www.tetsystems.com/
Amalgaam http://www.amalgaam.co.jp/
CLEA Japan Inc. http://www.clea-japan.com/
ICLAS Monitoring Center
http://www.iclasmonic.jp/annai.htm
Central Institute for Experimental Animals
http://www.ciea.or.jp/

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