Published in final edited form as:

Mamm Genome. 2012 October ; 23(0): 559–571. doi:10.1007/s00335-012-9420-4.

Centralized Mouse Repositories

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Abstract

Because the mouse is used so widely for biomedical research and the number of mouse models being generated is increasing rapidly, centralized repositories are essential if the valuable mouse strains and models that have been developed are to be securely preserved and fully exploited. Ensuring the ongoing availability of these mouse strains preserves the investment made in creating and characterizing them and creates a global resource of enormous value. The establishment of centralized mouse repositories around the world for distributing and archiving these resources has provided critical access to and preservation of these strains. This article describes the common and specialized activities provided by major mouse repositories around the world.

Keywords

mouse resources; repository; resource; biomedical research; genetics

Introduction: Practices Common to Most Repositories

For over a century the laboratory mouse has played a key role in understanding basic genetic principles, as well as understanding the genetics underlying mammalian biology and human genetic disorders. The mouse is recognized as an ideal model organism for biomedical research because of its many anatomical and physiological similarities to human beings. Use of mice also offers significant economic advantages as mice require less space and food than larger mammals and have a short gestation period, short lifespan, and rapid development.

Moreover, the long period of research using mice has resulted in a wealth of background data, specialized strain panels for genetic analyses, technologies for manipulating the mouse genome, and a rich base of literature on mouse genetics and biology. Finally, 95% of coding sequence in the mouse and human genomes is conserved, as shown when the mouse genome became the first non-human mammal to be sequenced in its entirety (Waterston and Consortium 2002).

Research with mice to understand genetics has led to the accumulation of large numbers of mouse strains – inbred, congenic, and spontaneous mutation strains, and strain panels. The advent of transgenic (Gordon et al. 1980) and gene targeting technologies (Mansour et al. 1988, Capecchi 1989), coupled with large scale mutagenesis (Hrabe de Angelis et al. 2000, Nolan et al. 2000) and gene trap programs (Nord et al. 2006) has led to an explosion in the production and use of mutant and genetically engineered mice. The value of targeting technologies for translational research is clear from a retrospective study showing a high correlation between targeted mutations of the top 100 drug targets and their phenotypes, mechanism of action, and resulting therapies (Zambrowicz and Sands 2003, Swinney and Anthony 2011). This value is corroborated by a recent comprehensive phenotypic assessment of a large number of mouse mutants generated by a gene-specific approach studying a large fraction of secreted and membrane protein putative drug targets (Tang et al. 2010). Large scale production programs such as the International Knockout Mouse Consortium (IKMC) – composed of the NIH-sponsored Knockout Mouse Project (KOMP), the North American Conditional Mouse Mutagenesis (NorCOMM) project, the European Conditional Mouse Mutagenesis (EUCOMM) Program, and the Texas Institute for Genomic Medicine (TIGM) – are well on the way to generating knockout mutations for all mouse genes (Austin et al. 2004) in embryonic stem (ES) cell lines, many of which are being used to produce novel mouse strains as the next step of the KOMP project (KOMP²) gets underway. The International Gene Trap Consortium (IGTC) offers embryonic cell lines that collectively represent mutations covering two-thirds of genes in mice (Skarnes et al. 2004). As genetic engineering continues to evolve, mouse models will become even more numerous and specialized in their use. Centralized repositories are essential if these valuable resources are to be securely preserved and fully exploited.

Ensuring the ongoing availability of these mouse strains preserves the investment made in creating and characterizing them and creates a global resource of enormous value. The establishment of centralized mouse repositories around the world for distributing and archiving these resources has provided critical access to and preservation of these strains. For investigators, repositories secure against loss of their strains, enable efficient and cost-effective colony management, reduce the number of mice used in research (consistent with the 3Rs promulgated by the United States National Institutes of Health – replacement, refinement and reduction), relieve them of using research dollars and interrupting research to distribute mice, help meet the NIH requirement for sharing research resources, and enable them to access a broad variety of strains and mutations for a variety of genes. Repositories make mice available to academics without licensing or reach-through encumbrances; in many cases, resources also are available to commercial, for-profit entities under a licensing or material transfer agreement.

The value of these repositories is reflected in usage of their resources by investigators around the world. Over the past 5 years, repositories in general have seen a steady increase in the number of mice and frozen materials requested, as well as the number of new strains submitted to be archived. For example, the number of orders at the Mutant Mouse Regional Resource Center (MMRRC) has increased an average of 7 percent each year during that period. The Jackson Laboratory (JAX) distributed nearly 100,000 live mice in 2011 and has already distributed almost 57,000 in the first half of 2012. In 2011 the MMRRC, JAX, Riken

BioResource Center (BRC) and Center for Animal Resources and Development (CARD) together distributed over 106,000 live mice and served over 2600 investigators worldwide. Likewise, the number of new strains deposited overall has increased at a similar rate. As examples, JAX accepted 389 in 2007 and 609 in 2011; the BRC, 3195 strains in 2007 and 4768 in 2011. While most repositories also distribute frozen embryos and sperm, orders for these materials are much fewer than for live mice and have not increased as dramatically. The statistics clearly show that investigators are using the repositories to archive their strains and that they prefer to receive live mice, whether from live colonies or recovered from the cryopreserved state.

Common repository activities are outlined below and include importation, preservation, curation, and distribution of mouse strains; implementing quality control programs to insure genetic stability (background) and fidelity (mutation), and optimal animal health status; and providing customer service and technical support for researchers using mice. In addition, different repositories may provide different levels and kinds of value-added mouse production, analytical, and phenotyping-related services.

Identify and evaluate mouse strains

Most repositories receive mouse strains submitted and deposited by individual investigators at academic institutions. Thus, the repositories have programs for evaluating and selecting strains to be imported. The first step in the selection process is investigator-initiated submission followed by a strain review process conducted by repository or external scientists with expertise in specific areas. Most repositories post an electronic submission form on their web site by which an investigator can submit a strain, learn about the requirements of the repository for acceptance, and the type of agreement for distribution. The strain submission process and subsequent interaction between repository personnel and the donating investigator collect information needed to make the strain useful to other investigators. Criteria used for acceptance include the uniqueness of the strain, the current and future importance of its use for research, the strength of the mutant phenotype, the validity of the model, whether the strain is the best model for its intended purpose, whether the mutant exists in another repository, and whether information about the strain or studies involving use of the strain have been published. The advantage of publication is that the strain has already been peer-reviewed and scientists will know about its potential scientific usefulness. Most repositories also will cryopreserve and archive strains for investigators on a fee-for-service basis.

Acquire and archive

Because most strains come from external sources, repositories have programs for importing the strains into high quality, secure facilities, using state-of-the-art rederivation methods to eliminate specific pathogens, and advanced cryopreservation techniques to safely store germplasm and embryos. Because animal room health statuses vary among research institutions, strains are rederived for 'specific pathogen free' (SPF) status or immediately cryopreserved during importation in the form of sperm or embryos. SPF recovery of these embryos or sperm is readily achieved by washing protocols (Suzuki et al. 1996, Stringfellow and Seidel 1998b). Some repositories cryopreserve embryos produced either by *in vitro* fertilization (IVF) (Renard and Babinet 1984) or mating of superovulated females (Mobraaten 1986). With improvements in preservation technologies, many strains are now preserved solely via sperm cryopreservation, whenever applicable, because it is much more economical than embryo cryopreservation as a means of archiving strains. Since the frozen archive need not be replenished as frequently with sperm cryopreservation, the cost savings can be passed on to the users (Ostermeier et al. 2008, Nakagata 2000, Takeo and Nakagata 2011). Sperm cryopreservation works well for strains carrying a single allele of interest, but

is not appropriate for cryopreserving compound mutants, inbred, congenic, or other strains with multiple alleles of interest; thus embryo cryopreservation is still used for such strains. The quality of cryopreserved materials is evaluated by reanimation of live mice and verification of their genotype. Once validated, new strains are made publicly available for distribution, often via a website, or sometimes a repository catalogue. Information about new strains also is often posted on a variety of common listservs.

For mutant mouse lines deposited and archived as embryonic stem (ES) cell lines, usually two vials of genotype-confirmed cells are required for importation. Typically, these are stored in separate tanks from embryos and sperm. ES cells often are not recovered until a request is received. All deposited cell lines are cryopreserved and processed to confirm viability and pathogen-free status prior to distribution to the scientific community. To maximize budgetary efficiency, testing usually occurs after an individual line is ordered and prior to distribution, at which point the line also can be expanded and banked in anticipation of future orders.

Distribution

Repositories distribute cryopreserved germplasm, embryos, and live mice according to the request of qualified investigators. Repositories also may provide reanimation (e.g., germplasm to live mice) and microinjection or aggregation (ES cells to live mice) services to facilitate distribution of live mice from inanimate, frozen archives. Repositories that ship cryopreserved germplasm and embryos usually provide user support information for sperm or embryo recovery. Most requests for strains held in the frozen state, however, are for live mice. Such requests are usually filled within 12–18 weeks depending on the repository and the strain. Live mice are shipped in filtered containers, to prevent environmental contamination, on dedicated trucks or by preferred live animal land carriers or airlines. Some repositories also distribute cryopreserved embryonic stem (ES) and induced pluripotent stem (iPS) cell lines. To distribute an ES cell line, a vial of frozen cells is thawed, then plated and grown up for expansion and Genetic Quality Control (GQC) evaluation and pathogen testing (if the latter were not done during the importation process). Repositories typically charge a fee to cover the cost of maintaining live colonies or resuscitating frozen materials, including ES cells, in addition to shipping costs.

Quality Control Programs

One of the advantages of centralized mouse repositories is their strict quality control programs, both for health status and genetic purity. Providing mice at the highest health standards also ensures that experiments are not confounded by pathogens and that studies are performed efficiently because time in quarantine is minimized or eliminated. In contrast, distributing mice from research colonies at different institutions, which often have variable health statuses, creates a risk of spreading pathogens among other research colonies. Repositories assure high animal health status in live colonies by surveillance programs with pathogen testing of sentinel or representative animals from the colony and by monitoring the environment in repository mouse rooms and material tracking. Repositories also have standard environmental conditions and operating procedures. Live mice recovered from a cryopreservation bank are essentially rederived to a high health status by the methods of collection and thawing of embryos or sperm.

Providing genetically defined and genetically stable mice to the scientific community ensures that experiments across laboratories and across generations can be replicated. Repositories implement genetic quality control programs to ensure genetic fidelity and stability. Mice arriving at the importation facility are genotyped as soon as possible to verify

that they carry the correct mutation. Some repositories also verify genetic background using panels of single nucleotide polymorphisms (SNPs).

Customer Service and Technical Support

Most repositories provide public web sites with strain and ES cell information (where appropriate) (see Box 1). Most also provide customer service and technical support to assist customers in selection of appropriate experimental models, and the form of material for delivery, i.e. frozen germplasm or live mice. Repositories take orders for mice or ES cell lines by either online or fax/telephone order systems. In addition to processing orders, customer service representatives typically provide investigators with basic information on strain and ES cell line availability, genotypes available, projected fulfillment times, fees, and basic technical information on strains and ES cell lines. Repository personnel also aid researchers in selecting the best mouse model for their own research.

Maintain standards that meet international repository standards

All repositories must meet minimum standards of animal care and use, as well as achieve a minimum health status, to be able to distribute mice. Most have high exclusion barrier facilities. All test for a set of specific pathogens although which pathogens are assayed may vary depending on the repository country's standards or those of various accrediting organizations. For example, the international Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) sets standards and accredits animal resource facilities in the United States and internationally. Similarly, the International Council for Laboratory Animal Science (ICLAS), which has members from all continents, also sets international standards for the care and use of animals including laboratory mice and the International Embryo Transfer Society provides guidelines to remove pathogens prior to embryo transfer (Stringfellow and Seidel 1998a).

Public Interface

Repositories provide a public interface to enable scientists to find, select, and request appropriate mouse strains, ES cell lines, and related services. Public web sites with mice and services available are backed by public databases with strain information, such as strain nomenclature, gene and mutation for mutant strains, strain background, and phenotype. Most repositories also list their mouse strains with the International Mouse Strain Resource (IMSR). The IMSR, which began as a collaboration between the Mouse Genome Informatics (MGI) group at The Jackson Laboratory and the Medical Research Council Mammalian Genetics Unit at Harwell, U.K., is a searchable online database that includes inbred, spontaneous mutation, and genetically engineered mice, and strain panels. The goal of the IMSR is to assist the international scientific community in locating and obtaining mouse resources for research. Box 1 provides a list of mouse repositories and related resources.

Provide Special Services

Most mouse repositories provide value-added research services to external investigators in the scientific community. Common services usually provided include cryopreservation, rederivation, breeding services such as speed congenics and contract breeding, disease diagnostics or histopathology, and genomic services such as genotyping, gene mapping, and scanning DNA markers across the entire genome. Many also provide selected forms of phenotyping, *in vitro* fertilization (IVF), and model development by targeted mutagenesis, transgenesis, and converting ES cells into mice.

Coordination among repositories

Repository personnel reviewing strains submitted for donation typically use as one criterion whether the strain or mutation is already available in a public repository to avoid duplication of effort, costs, and strain holdings. Repositories also share technology enhancements either directly or by publishing in the open literature. When a mouse line is not in its own holdings, a repository usually will enable customers to extend their search for strains held at other contemporary repositories, including the KOMP Repository, MMRRRC, and EMMA. For example, EMMA, has bilateral agreements with JAX and RIKEN BioResource Center (BRC) to ship frozen stock between repositories and locally rederive mice. In addition to such agreements with several EMMA partners, RIKEN BRC has similar agreements with The Jackson Laboratory, MMRRRC-UCDavis and the Canadian Mouse Mutant Repository (CMMR). Staff at EMMA and MMRRRC has been very helpful providing advice for the continued improvement of the Australian PhenomeBank (APB). Strains developed and characterized in Australia with funds from NIH and Wellcome Trust have been deposited with the MMRRRC and EMMA through a sharing arrangement with the APB, allowing US and European researchers direct access to these strains. Within the US, the MMRRRC (described below) is a well-established interactive consortium of 4 repositories strategically located in distinct geographic areas.

Research

Repositories frequently conduct research to enhance processes to import, cryopreserve, and distribute mouse strains efficiently and effectively or to enhance the value of models. Examples include improved protocols for sperm cryopreservation that increased recoverability of mice from sperm of different strain backgrounds, development of sperm cryopreservation kits, adaption of intracytoplasmic sperm injection (ICSI) to rescue strains with extremely low sperm quality, freeze-drying sperm as a means to ship sperm economically, development of line-specific genotyping assays, and additional phenotyping of mutant strains that broadens their utility. The transportation of frozen embryos offers many advantages over the shipment of live mice but it is still relatively expensive and relies on the recipient being able to handle the frozen embryos competently.

Provide educational and training programs

Finally, many repositories provide educational and training programs, either through formal coursework, collaboration with institutional training programs, or via visiting investigator programs. In addition, repository personnel lead workshops, produce webinars, and present talks and posters at national and international meetings.

Repository Profiles

Australian PhenomeBank

The Australian PhenomeBank (APB) was established in 2005 using funds provided by the National Health and Medical Research Council (NHMRC). In 2007, the formation of the Australian Phenomics Network (APN) with funding from the Australian Government's National Collaborative Research Infrastructure Strategy (NCRIS) and contributions from state governments and research institutes enabled the expansion of the services offered by the APB. An additional boost in funds was provided in 2009 from the Commonwealth's Super Science Initiative. The twelve Australian facilities and institutions that constitute the APN contribute their collective expertise and infrastructure to enable the scaled production and characterization of mouse strains. Cryopreservation operates at three nodes, The Australian National University (ANU), Monash University, and the Animal Resource Centre (ARC). Staff at the ANU node manages all client liaison, database curation, and maintenance. Many of Australia's key research institutes have contributed their strain

catalogues to the APB. As a result, not only do researchers have access to strains held in the archive, they can use the APB to identify strains held as a live colony elsewhere in Australia. Strain information submission, requests for cryopreservation, and requests for further information are made using an online system (Box 1). APB staff assists researchers meet nomenclature requirements before strain publication. The APB has provided training for staff establishing a cryopreservation service in New Zealand. APB staff participates in an education program run by the animal facility where animal technical staff is exposed to a snapshot of what happens in the laboratories.

Canadian Mouse Mutant Repository

The Canadian Mouse Mutant Repository (CMMR) was established at The Hospital for Sick Children in Toronto in March 2002 to support research and development in mouse-based cryopreservation and *in vitro* fertilization, and to establish a sperm and embryo biospecimen repository and distribution centre to support the Canadian functional genomics community. Re-located to the Toronto Centre for Phenogenomics (TCP) in 2007, the CMMR expanded its services to be the national repository for the NorCOMM-IKMC project and provides archiving, expansion, distribution, and downstream mouse model creation from the ES cells produced by the NorCOMM project. The CMMR currently has >350 knock-out and transgenic lines frozen as embryos or sperm, >40,000 gene trap and gene targeted NorCOMM ES cell lines, and >300 gene targeting and gene trap vectors available for distribution. The CMMR is co-located with the TCP's Transgenic Core, and the phenotyping and imaging programs of allied institutions so that a comprehensive resource of archive and distribution, *de novo* model creation, production and colony management, and phenotyping (*in vivo* and pathology) are integrated and available under one roof.

Center for Animal Resources and Development (CARD)

The CARD located at Kumamoto University was established in 1998 based on recommendations published in the report "Preservation, Supply and Development of Genetically Engineered Animals" by the Ministry of Education, Culture, Sports, Science and Technology in Japan and maintains web sites in both English and Japanese (Box 1). Card provides a comprehensive and integrated set of research services designed for the mouse-based biological research community. To promote biological sciences worldwide CARD produces genetically engineered mice and exchangeable gene trap ES cell clones, cryopreserves mouse embryos and sperm, supplies these resources, organizes training courses to educate people, and forms a hub of the domestic and international networks of both mutagenesis and resource centers. Up to now, CARD scientists have produced about 1,500 genetically engineered mouse strains and have more than 1,700 strains and stocks of mice for supply to the scientific community. As a founding member of the Federation of International Mouse Resources (FIMRe), the Asian Mouse Mutagenesis and Resource Association (AMMRA), and the International Knockout Mouse Consortium (IKMC), CARD is contributing to the promotion of biological sciences in the world. Information on submitting mouse strains to the CARD repository or obtaining resources from it may be found at the CARD web site (see Box 1).

Recently, CARD scientists developed a cryopreservation method for mouse sperm to obtain a very high fertilization rate (Takeo and Nakagata 2011). Mouse sperm frozen using this method can yield over 1,000 pups derived from frozen-thawed sperm collected from just one C57BL/6 male mouse via *in vitro* fertilization and embryo transfer techniques. This method will be very useful for the maintenance of genetically engineered mouse strains. In addition, cryoprotectant, preincubation medium, and fertilization medium for use in this method are available (<http://www.kyudo.co.jp/Fertiup/FERTOPen.htm>). CARD scientists also have demonstrated that frozen-thawed 2-cell embryos and 2-cell embryos produced by frozen-

thawed sperm and transported from our center to many institutes at a refrigerated temperature have the ability to develop well into live young (Takeo et al. 2009, Takeo et al. 2010). The advantages of this method are that the recipients do not have to master thawing techniques, and special containers (e.g., dry shippers) are not required for embryo transport. In the future, this method will be used by CARD to ship strains of genetically engineered mice.

European Mouse Mutant Archive (EMMA)

The non-profit EMMA repository network collects, archives, and distributes biomedically important mutant mouse stocks. EMMA has a network of 14 partners across Europe. EMMA is supported by member institutional funds, national funding programs, and the European Commission's Framework Programmes. Strain information for all EMMA strains, online submission and order forms, and links to the home page of individual EMMA members may be found at the EMMA web site (Box 1). EMMA offers as a special service the generation of germ-free (axenic) mice (<http://www.emmanet.org/axenic/intro.php>). EMMA also does research to establish the optimum conditions for transportation of unfrozen pre-implantation embryos across international boundaries. Furthermore, EMMA offers extensive training opportunities with currently five annual training courses. A comprehensive collection of up-to date protocols taught in the cryopreservation courses is displayed on the EMMA website. The EMMA archive currently comprises 3000 mouse mutant lines, among them the highly demanded EUCOMM mouse resource and the Wellcome Trust KO Mouse Resource. The EMMA mouse mutant collection can be searched by strains, genes, phenotypes, and human diseases (Box1).

European Mouse Mutant Cell Repository (EuMMCR)

The EuMMCR was founded in the framework of EUCOMM to collect, expand, archive, and distribute mutant ES cells and gene targeting vectors generated by the EUCOMM and EUCOMMTOOLS consortia as part of the IKMC. The current resource encompasses about 7000 targeted ES cell alleles and about 4300 gene trap ES cell alleles. Ordering information, standard ES cell handling conditions, quality control procedures, and blastocyst injection protocols are available at the EuMMCR web site (Box1). The EuMMCR is located at the Helmholtz Centre Munich, Germany.

Knockout Mouse Project (KOMP) Repository

In 2007, the U.S. National Institutes of Health (NIH) established a repository to archive and distribute mouse and ES cell lines produced by the Knockout Mouse Project (KOMP). The KOMP is a trans-NIH initiative that created a comprehensive and public resource comprised of mouse ES cell lines containing a null mutation in 8500 of the ~22,000 genes in the mouse genome. The KOMP program targeted genes by homologous recombination of conditional-ready knockout-first, targeted trap, and definitive null alleles in newly developed and improved C57BL/6 ES cells with robust germline transmission. Information and data generated by KOMP is collected and published online in a dedicated Data Coordination Center (DCC), which is freely accessible to the biomedical research community. KOMP production was funded by an NIH award to Velocigene, a division of Regeneron Pharmaceuticals, Inc., in Tarrytown, N.Y., and to a collaborative team from Children's Hospital Oakland Research Institute (CHORI) in Oakland, Calif., the School of Veterinary Medicine, University of California, Davis (UC Davis), and the Wellcome Trust Sanger Institute in Hinxton, U.K. A new NIH program, KOMP² (Knockout Mouse Production and Phenotyping), which began in 2011, seeks to convert all of the KOMP-targeted ES cell lines to homozygous mutant mice for comprehensive, high-throughput, broad-based phenotyping. Data and information from the KOMP² project will be made available online from a new international data center (iDCC). In addition, all targeting vectors, ES cells, mice, and

germplasm are available for distribution from the KOMP Repository (Box1), a joint venture between UC Davis and CHORI. In addition to distribution of products, the KOMP Repository offers value-added services, such as ES cell targeting, blastocyst microinjection of ES cells, cryopreservation and cryorecovery of germplasm, genetic quality control testing of ES cells and mice, germline transmission testing, colony management, and a host of other production and phenotyping services. KOMP and KOMP² are jointly funded by multiple NIH institutes, centers and offices.

Mouse Models of Human Cancers Consortium (MMHCC) Mouse Repository

The National Cancer Institute (NCI) established the MMHCC repository in Frederick, MD, in 2001 to make new mouse models of cancer more accessible to the research community. The MMHCC repository website (Box 1) displays strain information and an online strain submission form. Unlike most repositories, mice distributed from the MMHCC repository are available free of charge, although the requesting researcher is responsible for shipping charges.

Mutant Mouse Regional Resource Centers (MMRRC)

The MMRRC (Box1) was established in 1998 with NIH/NCRR funding to address the increasing need for mouse repository capacity (Battey et al. 1999)(Grieder 2002) in the United States. The MMRRC network consists of four repositories currently located at the University of North Carolina at Chapel Hill, the University of California at Davis, the University of Missouri at Columbia, and The Jackson Laboratory in Bar Harbor, Maine. The MMRRC focuses primarily on genetically engineered mice but accepts other mutant and inbred strains as well. The MMRRC also archives and distributes a large collection of mutant ES cell lines. An Informatics, Coordinating and Service Center (ICSC) is responsible for strain information management, customer service, and database development and maintenance. The MMRRC-ICSC provides a single interface to the public through a web site that displays strain information (Box 1) and access to an online strain submission form, searchable catalog, and online ordering form. The consortium of centers that make up the MMRRC offers the research community the collective expertise of these four institutions. Moreover, these institutions possess several unique programs and resources that naturally dovetail with the mission of the MMRRC, thus further strengthening their value to the research community. Examples of these unique resources include:

- The MMRRC-UCD provides access to the UC Davis Mouse Biology Program including ES and iPS cell derivation, gene targeting and screening, speed congenics, advanced genetic quality control testing, and pathology and other phenotyping services. Examples of research conducted include adaptation and development of ICSI for difficult to recover strains, preservation of sperm using non-conventional methods (freeze-drying and evaporative-drying), development of improved ES cell microinjection techniques, cryopreservation of oocytes and 1-cell stage embryos, and more.
- MMRRC-UNC provides access to strains of the Collaborative Cross (CC), which is a large panel of new recombinant inbred mouse strains(Churchill et al. 2004). The CC addresses many shortcomings in available recombinant inbred mouse strain panels, including small numbers of strains, limited genetic diversity, and a non-ideal population structure. The CC strains are derived from an eight way cross using a set of founder strains that include three wild-derived strains. The CC provides a translational tool to integrate gene functional studies, genetic networks, and variation maps of the biomolecular space. The beauty of the CC is its extensibility, providing a framework for cumulative data integration over space and time. In addition, the UNC MMRRC provides

advanced genetic quality control testing, pathology, phenotyping, and a panel of mutant ES cell lines that can be screened for mutations in a researcher's gene of interest. Examples of research include investigation of mechanisms of oxidative damage in cryopreserved mouse sperm, development of a SNP genotyping analysis tool, and epigenetics of germ cell development.

- The MMRRC-MU provides access to expertise in rodent genetics, diseases, mucosal immunology, and cryobiology with associated services in these areas such as karyotyping, phenotyping, and infectious disease diagnosis. For the latter, the MMRRC-MU collaborates with RADIL-IDEXX, the second largest rodent infectious disease diagnostic laboratory in the world, on development of novel processes and tests for infectious disease screening. The MMRRC-MU also collaborates closely with the National Rat Resource and Research Center (RRRC) and the National Swine Resource and Research Center (NSRRC). This collaboration provides efficiencies in center functions, but more importantly facilitates comparative studies for development and refinement of multiple species models and/or optimal selection of the most appropriate species for the modeling of specific diseases. Moreover, this collaboration facilitates studies requiring confirmation of phenomena across species that strengthen translatability of data obtained from a single species. Last, the MU-MMRRC provides an ideal forum for the training of scientists and laboratory animal veterinarians in the MU Comparative Medicine Program. These individuals are well-versed in the intricacies of management, care and use of complex genetic models of disease and often perform graduate research in laboratories of participating faculty. Examples of research emphasis areas include development of improved and economical methods of infectious disease screening and prevention, biology of rodent infectious agents, impact of microbes on rodent model phenotypes, and optimization of sperm cryopreservation and ICSI.
- MMRRC-JAX – The Jackson Laboratory has an extensive history in mouse genetics and husbandry expertise and a large repository that incorporates an MMRRC center (see below).

The Jackson Laboratory

The Jackson Laboratory (JAX) was established in 1929 as a non-profit genetic research institution and began to deposit and distribute strains to researchers almost immediately. Mouse strains held at JAX include inbred strains; spontaneous, chemically induced and genetically engineered mutant strains; recombinant inbred, congenic, and chromosome substitution (consomic) strain panels; and chromosome aberration strains. Except for high demand inbred and mutant strains, strains are distributed from the JAX Repository or the Cryopreservation Resource. JAX verifies newly imported genetically engineered mutations by allele-specific genotyping assays and verifies genetic background of all imported inbred or congenic strains using a SNP panel. For quality control, cryopreserved strains are recovered to live born pups, which are used to establish a distribution colony if researchers have expressed interest in the strain. One of the specialties at JAX is the capacity to maintain a large number of strains in live colonies and to produce and distribute large numbers of mice. Another strength is its expertise in reproductive science and cryopreservation. The Jackson Laboratory staff teach a colony management course several times a year, both on the JAX campus and at offsite institutions. JAX also provides a variety of other courses, conferences, and workshops with a variety of scientific themes throughout the year. Since 2004, JAX staff has contributed to the annual EMMA cryopreservation course held at the EMMA core facility at Consiglio Nazionale delle Ricerche (CNR) in Monterotondo, Italy. JAX has expanded its cryopreservation service using a Freeze Team and Sperm

Cryopreservation Kits. When a donating investigator has a large number of strains to cryopreserve, the Freeze Team - 2-3 Reproductive Sciences technicians - can be sent to the donating investigator's lab to cryopreserve sperm for shipment back to The Jackson Laboratory. For smaller numbers of strains, JAX will pick up the strains on set days and transfer them to the JAX importation facility for cryopreservation. The Sperm Cryo Kit is a further evolution of this concept in which the donating investigator is sent everything needed for cryopreservation and shipping of frozen material back to JAX. External funding for Repository strain programs began with NSF funding of the spontaneous mutant resource in 1960, and continued with NIH and foundation funding for induced mutants in 1992 and strain panels in 2001.

Information on all publicly available mouse stocks is accessible through a single database interface (JAX[®] Mice Database) found at the JAX website (Box 1). An online submission form for submitting strains also is available at the JAX website.

RIKEN BioResource Center (BRC)

The mouse repository at the RIKEN BRC, a non-profit institute, was formed in 2001 for the purposes of providing biological materials, technical services, and educational programs to private enterprises and academic organizations worldwide. The BRC specializes in inbred and mutant/genetically engineered mouse strains, various ES/iPS cell lines, and genetic materials such as bacterial artificial chromosome (BAC) clones of C57BL/6N and MSM/Ms, mainly developed in Japan. The BRC maintains a website both in English and Japanese (Box 1) that offers a database of mouse strain information. Scientists interested in depositing mice with the BRC or in obtaining resources from the BRC are urged to contact RIKEN BRC Experimental Animal Division: animal@brc.riken.jp. The BRC has initiated a research project to determine more economical and easier methods to distribute frozen materials internationally. RIKEN BRC has been conducting collaborative research with MMRRC-UCDavis and MRC Harwell to develop a secure method for international shipment of vitrified embryos of C57BL/6N in dry ice rather than using a vapor phase liquid nitrogen dry shipper. Costs for shipping, especially international shipping of frozen embryos and sperm using a dry shipper, are extremely high. Since the cost is covered by a recipient scientist's often limited research funds, scientists need a less expensive method of shipment. Recently, a commercial carrier started offering a less expensive shipping service, including arrangement of dry shipper equipment, so that repositories do not have to purchase their own equipment. This service is now well established for shipping between Japan and the U.S. and service to the rest of the world is now being tested.

Summary

In 2002 when Jonathan Knight and Alison Abbott wrote of the "logistical nightmare [of housing the burgeoning number of mice being created by genome manipulation] that is reaching crisis point" (Knight and Abbott 2002), the mutant strains being generated by ENU mutagenesis programs were just beginning to emerge, and the Collaborative Cross, which will generate hundreds of Recombinant Inbred strains, was only being planned (Churchill et al. 2004). The exponential increase in mouse strains has necessitated the enlargement of existing mouse repositories and the establishment of new ones. The increased centralized repository capacity and the major advancements in sperm cryopreservation have made archiving strains relatively economical and reliable and enabled the broad genomic coverage of mutant alleles maintained in ES cells that can be readily converted into live mouse lines. Continued funding for the repositories discussed in this review is critical for the efficient management of mouse strains developed today to take advantage of the technological breakthroughs of tomorrow. Finally, all the strains held by these repositories are accessible

through one portal – the IMSR – ensuring worldwide access to these valuable research resources.

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BOX 1

URLs for major mouse repositories and related resources

Table 1

Major mouse repositories and related resources with Universal Resource Locators (URLs).

<i>Repository/Resource</i>	<i>URL</i>
Australasia Repositories & Resources	
Asian Mouse Mutagenesis and Resource Association (AMMRA)	http://www.ammra.info/
<i>Some members are repositories while others are research institutes:</i> Bio-evaluation Center, KRIBB, Daejeon, Korea Biological Resource Centre, Singapore Center for Animal Resources and Development, Kumamoto University, Japan Institute of Developmental Biology and Molecular Medicine of Fudan University, Shanghai, China Institute of Laboratory Animal Science, CAMS&PUMC, Beijing, China Institute of Laboratory Animal Sciences of Peking Union Medical College, Beijing, China Laboratory of Cardiovascular Genomics of Ewha Woman's University, Seoul, Korea Nanfang Center for Model Organisms, Shanghai, China National Institute of Food and Drug Safety Evaluation, Seoul, Korea National Laboratory Animal Center, Taipei, Taiwan National Resource Center of Mutant Mice, Model Animal Research Center of Nanjing University, Nanjing, China RIKEN BioResource Center, Japan Seoul National University, Seoul, Korea Shanghai Institute for Biological Sciences, Shanghai, China	
Australian Phenomebank	http://pb.apf.edu.au/resources/mouse/sigtr/
Australian Phenomics Network	http://www.australianphenomics.org.au/
Bio-evaluation Center, KRIBB, Daejeon, Korea	http://www.kribb.re.kr/eng/sub02/sub02_04_06.jsp
Biological Resource Centre, Singapore	http://www.brc.a-star.edu.sg/
Center for Animal Resources and Development, Kumamoto University, Japan	http://cardb.cc.kumamoto-u.ac.jp/transgenic/index.jsp
Institute of Laboratory Animal Science, CAMS&PUMC, Beijing, China	http://www.cnilas.org/html/en/
National Institute of Genetics Mammalian Genetics Laboratory, Japan	http://www.nig.ac.jp/english/index.html
National Laboratory Animal Center, Taipei, Taiwan	http://www.narl.org.tw/en/tech/company/?company_id=5
National Resource Center of Mutant Mice, Model Animal Research Center of Nanjing University, Nanjing, China	http://www.en.nicemice.cn/default.asp
RIKEN BioResource Center, Japan	http://www.brc.riken.jp/lab/animal/en/
Shanghai Institute for Biological Sciences, Shanghai, China	http://www.sibs.ac.cn/en/
European Repositories & Resources	
European Conditional Mouse Mutagenesis (EUCOMM) programme	http://www.eucomm.org
European Mouse Mutant Archive (EMMA)	http://www.emmanet.org
<i>The EMMA website is the single EMMA user interface for all the EMMA partners</i> B.S.R.C. "Alexander Fleming", Varkiza (Athens), Greece Biocenter, University of Oulu, Oulu, Finland BIOCEV-Institute of Molecular Genetics (IMG), Prague, Czech Republic Biomodels Austria (BIAT), Vienna, Austria Centre National de la Recherche Scientifique, Transg�n�se et Archivage d'Animaux Mod�les (CNRS-TAAM), Orleans, France Consejo Superior de Investigaciones Cient�ficas, Centro Nacional de Biotecnolog�a (CNB-CSIC), Madrid, Spain Consiglio Nazionale delle Ricerche, (CNR), Monterotondo, Italy European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Hinxton, UK Funda��o Calouste Gulbenkian, Instituto Gulbenkian de Ci�ncia, Oeiras, Portugal Genome Research Limited, Wellcome Trust Sanger Institute (WTSI), Hinxton, UK GIE-Centre Europ�en de Recherche en Biologie et en M�decine, Institut Clinique de la Souris (GIE-CERBM-ICS), Illkirch-Strasbourg, France Helmholtz Zentrum M�nchen, Institute of Experimental Genetics (HMGU-IEG), Munich, Germany Karolinska Institutet, Department of Cell and Molecular Biology (KI-CMB), Stockholm, Sweden Medical Research Council, Mammalian Genetics Unit (MRC-MGU), Harwell, UK	
European Mutant Mouse Cell Repository	http://www.eummr.org/
Sanger Institute Gene Trap Resource	http://www.sanger.ac.uk/resources/mouse/sigtr/
Global Information Resources	

Repository/Resource	URL
American Association for Laboratory Animal Science (AALAS)	http://www.aalas.org
Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC)	http://www.aaalac.org/
International Council for Laboratory Animal Science (ICLAS)	http://www.iclas.org/
International Gene Trap Consortium	http://www.genetrap.org
International Knockout Mouse Consortium (IKMC)	http://www.knockoutmouse.org/
International Mouse Phenotyping Consortium (IMPC)	http://www.mousephenotype.org/
International Mouse Strain Resource (IMSR)	http://www.findmice.org/
Mouse Genome Informatics (MGI)	http://www.informatics.jax.org/
North American Repositories & Resources	
Allen Institute for Brain Science (AIBS)	http://www.alleninstitute.org/
American Type Culture Collection	http://www.atcc.org/
Canadian Mouse Consortium (CMC)	http://www.mousecanada.ca/
The CMC has Regional Resource Centers in Vancouver, Calgary, Winnipeg, Toronto, Ottawa, Réseau de Recherche en Transgénèse du Québec, Montreal and Halifax, which are all linked to the CMC web site.	
Canadian Mouse Mutant Repository (CMMR), Toronto, Canada	http://www.cmmr.ca/
Children's Hospital Oakland Research Institute (CHORI), Oakland, California, USA	http://bacpac.chori.org/home.htm
Gene Expression Nervous System Atlas (GENSAT)	http://www.ncbi.nlm.nih.gov/projects/gensat
Genetic Resource Science at JAX (GRS)	http://www.jax.org/grs/index.html
The Jackson Laboratory (JAX), Bar Harbor, Maine, USA	http://www.jax.org
Knockout Mouse Project (KOMP) Repository, University of California Davis, Davis, California, USA	http://www.komp.org
KOMP Data Coordination Center (KOMP-DCC)	http://www.komp.org/index.php?link=4
The Mouse Biology Program	http://www.mousebiology.org
The Mouse Brain Library	http://www.mbl.org/
Mouse Models of Human Cancers Consortium Mouse Repository (MMHCC), National Cancer Institute, Frederick, Maryland, USA	http://mouse.ncicrf.gov/
Mutagenetix, University of Texas Southwestern Medical Center, Texas, USA	http://mutagenetix.utsouthwestern.edu/
Mutant Mouse Regional Resource Centers (MMRRC)	http://www.mmrrc.org
<i>The MMRRC is a U.S. consortium comprised of four archive/distribution centers and an informatics center:</i> MMRRC-JAX, The Jackson Laboratory, Bar Harbor, ME MMRRC-MU, University of Missouri, MO MMRRC-UNC, University of North Carolina, Chapel Hill, NC MMRRC-UCD, University of California Davis, Davis, CA MMRRC-ICSC, University of California Davis, Davis, CA	
Neuromice Consortium (information source)	http://www.neuromice.org/
NIH Blueprint for Neuroscience Research	http://neuroscienceblueprint.nih.gov/
NIH Deltagen-Lexicon KO mice	http://www.mmrrc.org/about/Deltagen-Lexicon_links.php
North American Conditional Mouse Mutagenesis (NorCOMM) project	http://www.norcomm.org
Oak Ridge National Laboratory Collection (at JAX)	http://research.jax.org/grs/oak-ridge.html
Texas A & M Institute of Genomic Medicine (TIGM)	http://www.tigm.org