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BioResource now !

Our monthly newsletter features a variety of information, highlighting current domestic and international issues concerning bioresources.

Attention! Resources

Mouse Resources and Nobel Prize ～Part2～

Ken-ichi Yamamura, Professor,
Institute of Molecular Embryology and Genetics, Kumamoto University

Ongoing Column No.29

Flex has greatly enhanced the capabilities of Flash

Left to right: a rat, a mouse, and a harvest mouse

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- WGR http://www.shigen.nig.ac.jp/wgr/
- JGR http://www.shigen.nig.ac.jp/wgr/jgr/jgrUrlList.jsp

Announcements

(Details are available at http://www.nbrp.jp/index.jsp)

- Open recruitment for the "Program for the Maintenance and Improvement of Genome Information" conducted by NBRP for the fiscal year 2008
  Application Period: From March 3, 2008, to 17:00 on March 7, 2008.
- "NBRP Kick-off Symposium"
  Date : March 10 (Mon), 2008, 10:00 –17:00 at Josui Kaikan
- The 5th Workshop on Morning Glory
  Date : March 10 (Mon) 14:00 – March 11 (Tue) 12:15, 2008
  at Okazaki Conference Center (Medium Conference Room)
- NBRP Workshop on Algae (cryopreservation technology)
  Date : March 27 (Thur), 2008, 9:30 – 16:30
  at Medium Conference Room (National Institute for Environmental Studies/Seminar Room in the Environmental Species Preservation Building)

Attention Resources No.1 (2)

Mouse Resources and Nobel Prize ～Part2～

Ken-ichi YAMAMURA
Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

We have been conducting research, focusing on methods for gene-trap mutagenesis rather than homologous recombination. A gene-trap method involving embryonic stem (ES) cells was first reported in 1989—the year in which the first report on knockout mice was published. Since then, gene-trap mutagenesis has developed further as the preferred technique for generating knockout mice rather than for identifying genes. This is because homologous recombination is laborious, costly, and time-consuming, and the development of knockout mice by this method for all the mouse genes, which were then estimated to be 100,000 in number, was considered impossible. With the homologous recombination method, it is necessary to construct vectors one at a time; therefore, the probability of obtaining homologous recombinants among the ES clones is low, and the transfer of the recombinant genes to the germline is not guaranteed.

The International Gene Trap Consortium (IGTC), which we are a part of, was established in 2002. Since then, groups from Canada and Germany have undertaken large-scale projects for the development of mutant mice by using gene-trap mutagenesis. The promoter of projects involving homologous recombination is an ex-staff member of Dr. Martin Evans's laboratory, and the representative is Dr. Allan Bradly, who is currently the director of the Wellcome Trust Sanger Institute in the UK. In addition, most of the researchers involved in projects that employed the gene-trap method were staff members of Dr. Janet Rossant's laboratory. The representative of these projects was Dr. Wolfgang Wurst of the GSF-National Research Center for Environment and Health in Germany, who is a promoter of the European Conditional Mouse Mutagenesis (EUCOMM) project, and Dr. Bill Skarnes of the Wellcome Trust Sanger Institute. With these projects as the launching pad and triggered by the initiatives of EUCOMM, the following projects were launched: a large-scale knockout mouse project in EU in 2006, the North American Conditional Mouse Mutagenesis Project (NorCOMM) in Canada, the NIH Knockout Mouse Project (KOMP) in the US, and Chinese Conditional Mouse Mutagenesis (COMM) project in China. These projects have received a total funding of more than 10 billion Japanese yen. In total, 56,000 knockout ES clones and approximately 1,200 mouse strains are expected to be generated via homologous recombination and gene-trap mutagenesis under the IGTC project as a whole. This project is based on the awareness that resources are extremely important in the fields of fundamental and applied research and for potential industrial development. However, our country has displayed a lack of understanding towards resources.

Although this may not be the most pertinent example, a consideration of the requisites needed to engage in a war may throw light on the importance of resources. Our country traditionally prefers grandeur in battle but tends to neglect logistics support. It is impossible to win a war without the adequate supply of food, arms, and ammunition. Similarly, it is impossible to successfully conduct research without resources. The determination of genome sequences of various species was immediately followed by the post-genome era, wherein adequate attention was not accorded to resources. Consequently, it is now increasingly apparent that the analysis of genes and genome functions is not as simple as the determination of genome sequences. This turn of events highlights the indispensability of resources.

Unfortunately, gene knockout projects have not yet been initiated in our country, and the attention of researchers seems to have completely shifted toward the newly discovered induced pluripotent stem (iPS) cells. Nevertheless, gene knockout projects are by no means inferior to iPS research in terms of importance, and they should receive due attention. Gene knockout projects will be beneficial to almost every researcher in life sciences whereas iPs research will only benefit a selected few. We have developed a unique technology which is as effective as those developed in Europe and the US and which will undoubtedly yield results that are more significant when used to conduct projects for generating knockout mice. At the risk of sounding immodest, we must mention that we have developed an exchangeable gene-trap system, wherein a gene is completely knocked-out during the first phase, replaced with a gene of interest during the second phase, and conditionally knocked-out during the third phase. Although projects undertaken by Europe and the US employ a method that, in essence, can conditionally knockout genes, gene replacement in vitro is conducted by using a gateway system, and further homologous recombination should be performed by using the products. In our system, gene replacement can be performed via Cre-loxP recombination; thus, our method is extremely efficient and easy to perform.

Another advantage of our method is the fact that it employs the MSM/Ms strain, which is a wild mouse strain of the Mus musculus molossinus species and is native to Japan. This strain was developed by Moriwaki et al. after many years of research and was differentiated from C57BL/6 mice, which belong to the Mus musculus domesticus species, approximately 1 million years ago. Shiroishi et al. reported that the genome sequence of the MSM/Ms strain is approximately 0.8% different from that of the C57BL/6 strain and exhibits several unique phenotypes such as cancer resistance. We succeeded in establishing ES cell cultures of this strain and methods to effectively make genital disorders. The use of these ES cells and exchangeable gene-trap mutagenesis or homologous recombination can facilitate the development of unique resources that are not available in Europe or the US. Thus, the development of this strain as a mouse resource is a matter of pride for Japan.

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The notion that Asian ethnic groups generally neglect logistic support seems to be untrue. We founded the Asian Mouse Mutagenesis and Resource Association (AMMRA) (**Fig. 1**) in November 2006. The second meeting of this association was held in November 2007 to discuss the importance of mutagenesis and resources and we also managed to gather information regarding the circumstances prevailing in each country. Due to the economic situation in each country, the consolidation of resources has not progressed extensively. However, the developments achieved in this regard in China are particularly surprising: 100 million yuans have already been invested and another 100 million (200 million yuans in total, i.e., 3–3.2 billion Japanese yen) will be granted as funding for projects involving mutagenesis. In addition, large-scale facilities are under construction, and within a short period of time, China will supercede Japan with regard to such research.

Finally, we present information regarding patents for homologous recombination systems, which, surprisingly, many people are unfamiliar with. Currently, the basic patents for homologous recombination systems are held by the Pasteur Institute, which Dr. Le Mouellie and Dr. Brulet are affiliated to, and the licenses are held by Cellectis, a venture firm of the institute. The patents are valid in Europe, the US, and Japan. The patent held by Dr. Capecchi applies to positive-negative selection methods and is only valid in the US. Private companies that are commissioned to manufacture knockout mice via homologous recombination or those that develop drugs using these mice infringe these patents. TransGenic Inc. is the only company in Japan licensed to perform these activities.

① **Biological Resource Center, Singapore**
② **National Laboratory Animal Center, Taipei**
③ **National Resource Center for Mutant Mice, Nanjing Univ. Nanjing**
④ **Shanghai Institute of Biological Sciences, Shanghai**
⑤ **Nanfang Center for Model Organisms, Shanghai**
⑥ **Peking Univ.-BLARC, Beijing Inst. Laboratory Animal Science, CAMS, PUC, Beijing**
⑦ **Bio-Evaluation Center, KRIBB, Daejeon**
⑧ **Riken BioResource Center, Tsukuba**
⑨ **Center for Animal Resources and Development, Kumamoto**

AMMRA Website

Fig.1 Members of AMMRA

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Flex has greatly enhanced the capabilities of Flash

Flash is generally used for simple animation and movie distribution; however, the emergence of Flex has greatly enhanced the capabilities of Flash.

The term **Flash** carries different connotations depending on which of the following contexts is used.

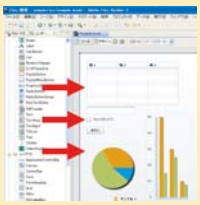
- Flash content
- Software required to create Flash content
- Environment required to run Flash programs (Flash Player)
- General term to describe all of the above

Flex is a framework designed to easily develop Flash content with practical applicability. Files created by both Flash and Flex have the extension ".swf" and must be run on Flash Player.

Practicality: As a default setting, Flex provides web developers the Flash version of HTML components such as tables and buttons (including functions that are unique to Flash) that are necessary for web applications.

Although Flash can be used to display a wide variety of contents, some users find it difficult to operate. However, Flex has set a certain standard in regard to its components and Flash is now also being used in practical websites.

Easy development: A software package known as Flex Builder (Adobe) is used to develop Flash content. With the Flex Builder program, components provided by Flex can be used by the drag-and-drop option (see **Fig.**).
A trial version of Flex Builder is available and is freely distributed to students and educational institutions; therefore, please download it and attempt to develop Flash content. Further, please refer to the samples that have been developed by using Flex Builder (Shingo Sakaniwa).



(Fig.) Operation screen of Flex Builder. Components can be used by the drag-and-drop operation.

http://www.shigen.nig.ac.jp/shigen/news/n_letter/2008/2/sample.html

A Request to Researchers

We have a request to researchers who uses our bioresources for their research. Please include information of the resources in Materials & Methods or Acknowledgement when you publish your research journals. In addition, please contact the source of your resources.

NBRP has opened a registration website for research journals. You can easily submit your information at the address provided below.

http://rrc.nbrp.jp/

Editor's Note: As a continuation of the previous month's issue, the second half of Dr. Yamamura's article "Mouse Resources and Nobel Prize" has been included in this issue. Impassioned messages based on his extensive view of the world, foresight, and advanced technological skills were conveyed to us. We also appreciate his comments regarding the encouragement of logistic support (Y.Y.).

Coming up in the next issue !
The special topic on resources discussed in next month's issue will be **"Cellular Slime Molds"**.

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